Universität Basel
Fakultät für Psychologie

“I wish I had better news”:

Psychological distress, risk factors and professional physician-patient communication in hospitalized patients and their relatives

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Abstract

Introduction: Falling ill and being hospitalized is a significant experience in any person's life, which oftentimes not only entails physical, but also psychological sequelae. This thesis aims at studying psychological distress, risk factors, and professional physician-patient communication in patients with high prognostic uncertainty and high risk for mortality.

Methods: Several methodological approaches were used: two prospective observational cohort studies to assess psychological distress and long-term health impairments, as well as risk and protective factors in COVID-19 patients and relatives and out-of-hospital cardiac arrest patients; a systematic review and meta-analysis to assess medical futility for CPR on IHCA patients' definitions, measures and association with do-not-resuscitate code status and evaluation of predictive values of clinical risk scores; a narrative review to assess the effect of stress on CPR performance in resuscitators; and a randomized controlled trial to evaluate an E-learning tool's aid in enhancing communication techniques in breaking bad news.

Results: In both studies on psychological distress after COVID-19 infection, patients and relatives are similarly affected by psychological sequelae at 1- and 3-month follow-up with prevalences of psychological distress, anxiety, depression, and PTSD symptoms ranging between 18.3%-22.9%, 14.2%-17.5%, 7.9%-15%, and 2%-8.7%, respectively. Several sociodemographic, psychosocial, and hospital-related factors were associated with psychological distress at one and three months after hospitalization, with risk factors such as perceived stress and overall burden, social connectedness, and resilience recurring over both time points in patients and relatives.

Concerning findings on cardiac arrest, we found that 50% of OHCA survivors suffered from long-term impairments including 37% in the physical domain, 25% in the cognitive domain and 13% in the psychological domain, with similar prevalences at 12-month follow up. Further, several partially modifiable risk factors were identified. When aiming to identify patients in which CPR may be deemed futile, several pre-arrest risk scores were identified with good prognostic value for poor neurologic outcome/in-hospital mortality in the meta-analysis (6 studies, 115213 participants with GO-FAR and PIHCA score; RR 6.93 [95% CI 6.43-7.47]). Further, in the narrative review we found that resuscitators' stress levels are associated with resuscitation performance and identified only few interventional studies that aim to reduce this effect.

Last, we found that an E-learning assignment could improve medical students' accurate recognition of communication techniques for breaking bad news concerning inappropriate communication elements (2.33 [2.57] versus 3.33 [3.39], p = 0.037).

Discussion: Illness and hospitalization do not only entail physical impairment, but also psychological distress in a relevant proportion of critically ill patients long after hospital discharge. However, during hospitalization several risk factors can be considered, which can help preventatively target at-risk patients or modify treatment for these patient groups. Further, appropriate communication of bad news and risk communication is of vital importance and can be improved through targeted communication strategies and clearly defined risk factors to be able to reduce potential uncertainty and distress during medical treatment.

1 Theoretical Background

Falling ill and being hospitalized is a significant experience in any person's life. While treatment for the somatic illness is ongoing, concerns about health and uncertainty about future life plans are oftentimes highly present in patients and their relatives and pave the way for possible psychological sequelae. This uncertainty, being a perceptual state of doubt and sense of loss of control, can include many aspects of illness such as prognosis or treatment recommendations, but may also touch on existential and psychosocial issues (Johnson Wright et al., 2009). Illness induced uncertainty has been found to be associated to psychological problems and maladaptive coping in patients and their relatives (Mullins et al., 2001; Szulczewski et al., 2017). This is especially true for critically ill patients. Psychological distress, such as depression, anxiety and post-traumatic stress disorder (PTSD) are highly prevalent in intensive care unit (ICU) survivors (Davydow et al., 2009; Hatch et al., 2018). Similarly, close relatives of critically ill patients oftentimes suffer from similar psychological symptoms (Fumis et al., 2015; Gil-Juliá et al., 2021). These adverse effects may be alleviated either by implementing prognostic scores to better communicate further management and potential consequences, or by enhancing patients' understanding, for instance through communication and self-management interventions (Etkind & Koffman, 2016; Stiegelis et al., 2004; Wolyniec et al., 2022). Hereinafter, psychological distress in patients with high prognostic uncertainty and high risk for mortality, as well as prognostic factors and professional physician-patient communication will be discussed.

1.1 Long-Term Impairments after Critical Care

Post-intensive care syndrome (PICS) summarizes long-term impairments which can occur after suffering from a critical illness. PICS is often defined as new or aggravated dysfunction(s) in the physical, cognitive and/or mental (psychiatric) domain after critical illness (Preiser et al., 2020). Attempts for an accurate definition are still ongoing, nevertheless, it is becoming a more frequently used concept in current clinical practice (Turnbull et al., 2016). The need for accurate definition of this newly emerging syndrome is high, seeing as ICU survivors' long-term physical, neurological and mental health status have become increasingly concerning in recent years (Morgan, 2021).

Current research indicates that more than 50% of ICU survivors may suffer from at least one component of PICS (Marra et al., 2018; Morgan, 2021). This may be due to therapeutic advances in intensive care medicine, which result in a higher number of ICU survivors, yet with a concurrent steady increase of patients' age and comorbidities upon ICU admission (Kim et al., 2019). Physical impairments in ICU survivors often entail impairments in body functions,

activity limitations and physical weakness (Appleton et al., 2015; Ohtake et al., 2018). Further, memory and executive functions are frequently affected in cognitive impairments of ICU survivors (Hopkins & Jackson, 2006). Psychological distress, such as anxiety, depression and post-traumatic stress disorder (PTSD) are also frequently found (Hatch et al., 2018). Still, research is sparse on the interrelations of this newly emerging syndrome.

1.2 Psychological Distress in COVID-19 Patients and Relatives

The novel Coronavirus disease 2019 (COVID-19) has caused a global pandemic with far-reaching implications for many aspects of society. While some patients have asymptomatic courses, many patients with COVID-19 experience mild flu-like symptoms and some patients may develop an acute respiratory distress syndrome (Guan et al., 2020; Lescure et al., 2020). Children and healthy young adults are often less affected by the disease, yet vulnerable individuals such as the elderly, people with chronic lung disease or cardiovascular comorbidities are at high risk of experiencing complications needing invasive ventilation or circulatory support (Bhatraju et al., 2020; Qiu et al., 2020). Further, studies suggest that COVID-19 causes a relevant increase in risks of excess mortality and morbidity in any period of the pandemic (Armstrong et al., 2020; Faust et al., 2022; Richardson et al., 2020; Woolf et al., 2021). As a newly evolved infectious disease, it has caused uncertainty for the health care system, as well as ultimately patients and families concerning etiology, prognosis, progression and adequate treatment (Koffman et al., 2020).

Yet, previous epidemics have shown that people are not only at risk of somatic morbidity but may also be prone to mental health issues. For instance, previous similar epidemics caused by coronaviruses such as the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) showed affected patients to be at risk for mental disorders, including depressive and anxiety disorders, PTSD, and sleep disorders (Rogers et al., 2020). Further, studies found prevalence rates from 10% to 50% for depression or anxiety in COVID-19 survivors (Krishnamoorthy et al., 2020; Liu et al., 2020; Mazza et al., 2020; Tomasoni et al., 2021) and pooled prevalences of 24% for PTSD symptoms (Cooke et al., 2020), suggesting persisting psychological distress in a considerable number of patients. Also, relatives of COVID-19 patients might be equally affected by psychological distress (Dorman-Ilan et al., 2020), but evidence is scarce.

Further, in spring of 2020, most countries, including Switzerland, implemented orders of at-home isolation or other quarantine measures to contain the spread of COVID-19. Consequently, hospitalized patients with COVID-19 were often quarantined and visits were strictly limited. Research during previous pandemics have shown that isolation measures similar to the ones used to contain COVID-19 suggest a negative impact on psychological well-

being with adverse psychological effects on patients and relatives (Brooks et al., 2020; Maunder, 2003; Rubin & Wessely, 2020; Tsang et al., 2004). During the beginning of the pandemic, a large Swiss study surveying the general population found an increase in the prevalence of depressive symptoms from 3.4% before the pandemic to 9.1% during confinement, 11.7% during partial deconfinement, and 18% during the second wave (de Quervain, Aerni, Amini, Bentz, Coynel, Gerhards, Fehlmann, et al., 2020; de Quervain, Aerni, Amini, Bentz, Coynel, Gerhards, Freytag, et al., 2020). Similar increases of psychological distress were also found in other countries at the time (Bäuerle et al., 2020; Daly et al., 2021; Twenge & Joiner, 2020).

With the observed rise of psychological distress at the beginning of the pandemic, and COVID-19 patients and relatives being especially at risk, the need for identifying prevalence and risk factors for psychological distress in this group is high. Some research indicated that risk factors for psychological distress may include different sociodemographic, illness-related, psychosocial and hospital-related characteristics (Luo et al., 2020; Rogers et al., 2020). Yet, also potential protective factors such as individual resilience, often defined as a person's emotional and mental capacity to adapt well when experiencing critical life events (Holz et al., 2020; Russo et al., 2012; Southwick & Charney, 2012), may aid in a pandemic with high uncertainty, seeing as resilience has been shown to correlate positively to mental health (Hu et al., 2015).

COVID-19 as a new and therefore poorly understood disease poses high uncertainty and challenges for adequate medical treatment, but also for the mental health of the individuals directly affected. Therefore, fundamental research on psychological sequelae and its risk factors in COVID-19 patients and their relatives is needed.

1.3 Long-Term Impairments in Cardiac Arrest Patients

Cardiac arrest is the sudden cessation of cardiac activity, i.e. effective ventilation and circulation leading to unresponsiveness and unconsciousness of the victim (Patel & Hipskind, 2022). It can progress to sudden death if not treated promptly, i.e. immediate start of cardiopulmonary resuscitation (CPR) (Patel & Hipskind, 2022). Cardiac arrest is an important cause of death worldwide (Benjamin et al., 2019). However, the prognosis still is poor with only 25% of patients returning to a spontaneous circulation (ROSC) and approximately 10% of patients leaving the hospital alive (Jentzer et al., 2016; Wong et al., 2014).

There are two different conditions in which a cardiac arrest can occur: the out-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA). Concerning IHCA, around 17% to 22% of patients survive to hospital discharge (Ebell & Afonso, 2011; Ohlsson et al., 2016; Peberdy et al., 2003) and 13.4% survive up to one year later (Schluep et al., 2018). OHCA

patients, on the other hand, show survival rates to hospital discharge of around 8% (Sasson et al., 2010; Yan et al., 2020). Survival rates have steadily improved in IHCA and OHCA patients over the decades (Virani et al., 2020; Yan et al., 2020) and while survival rates of IHCA patients are still improving to date, the proportion of ROSC following OHCA that is attended by emergency medical services and transported to the hospital alive remain unchanged over the past decade (Virani et al., 2020; Wong et al., 2014). Also, especially in patients with preexisting severe illness and/or debilitating comorbidities survival to discharge with a favorable neurologic outcome in case of a cardiac arrest is highly unlikely, and CPR may be considered medically futile (Ebell & Afonso, 2011). The potential harm of futile CPR may be grave with an increased chance for patients for disability, prolonged ICU stay, anoxic brain injury or nursing home placement (Blinderman et al., 2012). Yet, concrete criteria to determine medical futility for CPR is largely lacking and implementation in clinical practice remains difficult.

Further, the quality of resuscitation is vital for survival of cardiac arrest (Talikowska et al., 2015). Especially the standardization of CPR and post-arrest care through the implementation of rapid and effective resuscitation have led to improvements of survival with good neurological function (Girotra et al., 2012; Jentzer et al., 2016). Nevertheless, CPR is a substantial challenge for involved healthcare professionals and consequently, rescuers may experience high levels of acute mental stress. Acute stress has been shown to potentially reduce attentional resources (Hockey, 1997) and increase distractibility (Braunstein-Bercovitz et al., 2001; LeBlanc, 2009), therefore potentially impairing resuscitation performance (Hunziker et al., 2011; Hunziker et al., 2013; Krage et al., 2017) and subsequently possibly resuscitation outcome. Contrarily, research has also shown that during challenging situations individuals are capable of protecting their resources allocated to a primary activity from stress (Hockey, 1997). Therefore, it is unclear which mechanisms and interventions are associated with stress and CPR performance.

The abovementioned risk factors all potentially increase the risk of long-term impairments and, due to oftentimes necessary intensive care, increasing the risk for PICS. In fact, a substantial part of IHCA patients experience lower health related quality of life than population norms, especially having problems with pain, mobility and daily life activities (Israelsson et al., 2017; Schluep et al., 2022). Similarly, OHCA survivors often demonstrate worse physical and social functioning than the general population with 18% having moderate disabilities and 12% poor autonomy (Chin et al., 2022; Peskine et al., 2021). Further, neurological and cognitive disabilities are frequent, with neurologic impairments in IHCA patients ranging between 23% and 44% (Girotra et al., 2012; Peberdy et al., 2003) and OHCA patients generally estimated to occur in 42% to 50% of patients (Moulaert et al., 2009).

Psychological distress is also prevalent with approximately one in four cardiac arrest survivors estimated to have psychiatric disorder with depression (12.6%) and anxiety disorders (10%) being most common (Desai et al., 2019). Yet, to date, not much is known about presenting PICS in this patient group.

Several well-known risk factors for long-term health impairments after OHCA exist, such as low-flow time, clinical severity at ICU admission, prolonged coma duration, and mechanical ventilation (Peskine et al., 2021). Also, young age and female gender was associated with higher risk for poor health and for comorbid psychiatric disorders in cardiac arrest patients (Desai et al., 2019; Israelsson et al., 2017; Viktorisson et al., 2019). Yet, further knowledge of risk factors could improve adequate future screening and treatment of cardiac arrest survivors.

1.4 Communication Skills for Professional Patient-Physician Interaction

Critical illness, with following physical impairments and psychological distress, affords professional communication skills from physicians. These communication skills include patient-centered communication with the goal of involving the patient more strongly in the consultation and decision-making process (Dowsett et al., 2000). Patient-centered communication provides not only medical information but also emotional support and emphasizes exploring the patient's concerns, medical concepts and responding to those in a manner which is fit to the patient's needs (Mast et al., 2005; Sparks et al., 2007).

Especially concerning critical illnesses, physicians are faced with situations of having to break bad news. Bad news in the medical field is defined as "any information likely to alter drastically a patient's view of his or her future" (Buckman, 1984). Communicating information with such high impact upon a patient's life continues to be one of the most challenging communicative situations for physicians (Dosanjh et al., 2001; Ramirez et al., 1995). Therefore, different techniques for breaking bad news (BBN) have been developed, such as the SPIKES model (Baile et al., 2000), the ABCDE model (VandeKieft, 2001) or the BAD scheme (Becker et al., 2019). These techniques all base on patient-centered communication (Mast et al., 2005), which on the one hand help physicians communicate with a clear structure, on the other hand adhere to patients' needs. It has been shown that poorly communicating bad news may result in patient distress or confusion (Butow et al., 1996; Roberts et al., 1994). Contrarily, if it is communicated effectively, patients are more likely to adjust to the situation and lower the psychological burden in patients and relatives (Abazari et al., 2019; Fallowfield & Jenkins, 2004; Lautrette et al., 2007).

The BAD scheme, one of the BBN communication techniques, is an acronym standing for "Break bad news", "Acknowledge the reaction" and "Discuss the near future" (Becker et al., 2019; Schmid Mast et al., 2005). The communication technique instructs the physician to, first,

deliver the message by making sure to have all necessary information available, announce the bad news by a warning shot to allow the patient to prepare for the following information, and to deliver the diagnosis in a clear and simple manner following the Keep it short and simple (KISS) principle. Second, the patient should be offered enough time to process the bad news and the physician should acknowledge the patient's reactions by offering more information when requested or responding to emotions if the patient shows signs of psychological distress. Last, the physician should communicate the next steps clearly and a follow-up meeting should be scheduled (Becker et al., 2019).

Even though adequate communication of bad news is pivotal, it is also one of the most challenging communicative situations for physicians (Dosanjh et al., 2001; Ramirez et al., 1995). As training the communicative skill of BBN has shown positive results (Daetwyler et al., 2010; Langewitz, 2017), an effective and easy accessible way of teaching BBN must be sought.

2 Aim of the Thesis

This thesis is aimed towards demonstrating the prevalence of physical and psychological sequelae in critically ill patients and with a high uncertainty of the prognosis: COVID-19 patients and their relatives, as well as cardiac arrest patients. Further, this thesis aims to discuss possibilities to reduce this physical and psychological sequelae by 1) assessing risk and protective factors in these patient subgroups in short-, middle- and long-term to enable easier identification of at-risk patients and identify modified treatment options and 2) by developing and testing blended learning as a viable tool to teach breaking bad news.
To this end, the following studies have been conducted:

Study I: Prevalence and Factors Associated with Psychological Burden in COVID-19 Patients and their Relatives: A Prospective Observational Cohort Study.
Study II: Psychological Burden in Patients with COVID-19 and their Relatives 90 Days after Hospitalization: A Prospective Observational Cohort Study.
What is the prevalence of psychological distress in COVID-19 patients and relatives and what are potential risk and protective factors?

Study III: Post-Intensive Care Syndrome in Out-of-Hospital Cardiac Arrest Patients: A Prospective Observational Cohort Study.
What is the prevalence of PICS in OHCA patients and what are potential risk factors among physical, cognitive and psychological symptoms?

Study IV: Medical Futility Regarding Cardiopulmonary Resuscitation in In-Hospital Cardiac Arrests of Adult Patients: A Systematic Review and Meta-Analysis.
How is medical futility for CPR in adult patients defined, measured and associated with DNR code status?

Study V: Does Stress Influence the Performance of Cardiopulmonary Resuscitation? A Narrative Review of the Literature.
How is does stress influence CPR performance and which interventions can reduce this association?

Study VI: Breaking Bad News: A Randomized Controlled Trial to Test a Novel Interactive Course for Medical Students Using Blended Learning.

Can an E-learning assignment improve medical students' accurate recognition of BBN communication techniques?

3 Methods

3.1 Two Prospective Observational Cohort Studies

3.1.1 Prevalence and Risk Factors Associated with Psychological Distress in COVID-19 Patients and Relatives

Study setting and population: This exploratory, prospective observational two-center cohort study was conducted at the University Hospital Basel and the Kantonsspital Aarau from March until June 2020. All patients consecutively admitted with COVID-19 and their closest relative were eligible for inclusion into this study. Exclusion criteria for patients and relatives were insufficient knowledge of the local languages, cognitive impairment, or serious psychiatric conditions. Further, relatives and patients were excluded if no informed consent was provided.

Data collection: Data was obtained by telephone interviews and hospital medical records. We contacted relatives during hospitalization, and patients and relatives one and three months after hospital discharge for telephone interviews.

Predictor variables: We assessed potential predictor variables from four domains, i.e., sociodemographic, illness-related, psychosocial and hospital-related factors. While items in the sociodemographic domain were the same for both patients and relatives, factors in the other three domains partially differed to account for patient- and relative-specific characteristics. Predictor variables were assessed at hospital admission and/or one month after hospital discharge.

Outcome variables: All outcome variables were collected 30 and 90 days after hospital discharge. The primary endpoint, psychological distress, was defined as clinically relevant symptoms of anxiety and/or depression, measures by the Hospital Anxiety and Depression Scale (HADS) with a cut-off score of ≥ 8 on the depression and/or anxiety subscale (Bjelland et al., 2002; Zigmond & Snaith, 1983). The secondary endpoint, symptoms of PTSD, was assessed through the Impact of Event Scale-Revised (IES-R) with a cut-off score of 1.5 (Creamer et al., 2003; Maercker & Schützwohl, 1998).

3.1.1.1 Psychological Distress in COVID-19 Patients and Relatives 30 Days after Hospital Discharge

Statistical analysis: All analyses were conducted separately for each the patient and the relative sample. We stratified the two samples based on the presence or absence of psychological distress at the predefined cut-off. First, we calculated univariate logistic regression models for the primary and secondary endpoint and then adjusted for age, gender and study center. Second, we calculated a multivariate logistic regression for each domain, resulting in four models. These included predefined factors for each domain, as well as all

factors significantly associated in the previous, age-, gender- and study center-adjusted analyses. Third, to evaluate which factors might be independently associated with psychological distress, we analyzed an overall model containing all factors significantly associated with psychological distress within the four domain models.

We calculated odds ratios (OR) and 95% confidence intervals (CI). To account for missing data in predictors used in the multivariate analyses, we imputed datasets using multiple imputations by chained equations. A p-value of < .05 (two-tailed) was considered significant. Areas under the curve (AUC) were created to evaluate the potential prognostic value of the factors regarding psychological distress. All statistical analyses were conducted using Stata 15 (Stata Corp, College Station, Texas, USA).

3.1.1.2 Psychological Distress in COVID-19 Patients and Relatives 90 Days after Hospital Discharge

Statistical analysis: Data were analyzed separately for the patient and relative sample. Samples were stratified based on the presence or absence of psychological distress at the predefined cut-off.

We calculated univariable logistic regression models for the primary and secondary endpoint. We did not conduct multivariable analyses to avoid overfitting due to the lower number of endpoints. OR and 95% CI are shown as a measure of association and AUC as a measure of discrimination. We calculated an AUC of a combined regression model with all factors significantly associated with the primary outcome in the univariable analyses to understand the potential predictive value of the identified risk factors. A p-value of <.05 (two-tailed) was considered statistically significant. All statistical analyses were conducted using Stata 15 (Stata Corp, College Station, Texas, USA).

3.1.2 Prevalence and Risk Factors for Post-Intensive Care Syndrome in Out-of-Hospital Cardiac Arrest Patients

Study setting and population: This study was part of the COMMUNICATE trial, an ongoing prospective observational cohort study at the ICU of the University Hospital Basel investigating the prognosis and long-term outcomes in cardiac arrest patients. We consecutively included adult patients admitted to the ICU after OHCA and who participated in the 3-month and/or 12-month follow-up assessment. No exclusion criteria regarding patient characteristics were used.

Data collection: Data were prospectively collected upon ICU admission. Patients' medical characteristics were extracted from hospital medical records. We conducted

structured telephone interviews with patients 3 and 12 months after ICU admission to evaluate outcomes.

Predictor variables: At ICU arrival, we collected predictor variables from hospital medical records, such as patients' sociodemographic information, setting of and reason for cardiac arrest, ICU treatment received, comorbidities, and ICU and hospital length of stay. Clinical scores were calculated at ICU arrival as suggested in original publications (Adrie et al., 2006; Knaus et al., 1985; Le Gall et al., 1993; Maupain et al., 2016). After discharge, we assessed the number of weeks in rehabilitation and working status three months after hospitalization.

Outcome variables: The primary outcome PICS was defined as symptoms or impairment in at least one of the following domains: physical impairment, cognitive impairment and/or psychological distress (Preiser et al., 2020). Physical impairment was evaluated with the EuroQol questionnaire (EQ-5D-3L) assessing general health-related quality of life and used a cut-off score of ≤0.8 to determine relevant physical impairment (EuroQol, 1990). Cognitive impairment was assessed with the Cerebral Performance Category (CPC) (Jennett & Bond, 1975) and the modified Rankin Scale (mRS) (Quinn et al., 2009). For the CPC score, which measures patients' neurological status, we considered level 1 and 2 as favorable neurological outcome, whereas level 3 to 5 were defined as poor neurological outcome (Adrie et al., 2006; Maupain et al., 2016). For the mRS scale, we considered levels 0 to 3 as favorable outcome; levels 4 to 6 were defined as unfavourable outcomes (Quinn et al., 2009; Rittenberger et al., 2011). Psychological distress was defined as clinically relevant symptoms of anxiety, depression and/or PTSD. Symptoms of depression and anxiety were assessed with the HADS, with a score of ≥8 on the depression and/or anxiety considered as clinically relevant (Bjelland et al., 2002; Zigmond & Snaith, 1983). PTSD symptoms were assessed by the IES-R with a cut-off score of 1.5 (Creamer et al., 2003; Maercker & Schützwohl, 1998).

Statistical analysis: To evaluate associations between potential risk factors and the occurrence of PICS at 3- and 12-month follow-up, logistic regression analyses were performed for the primary endpoint and separately for the three domains of PICS. As a measure of association, OR and 95% CI are reported. In addition, univariable logistic regression analyses were adjusted for age and gender. We did not perform further multivariable analyses due to the low number of events to avoid overfitting. Further, a chi-square test and cross-tables were used to determine the persistence of patients with PICS between 3- and 12-month follow-up. Pearson correlations were calculated between the three PICS domains in a correlation matrix at 3 and 12 months. Stata 15 (StataCorp, College Station, Texas, USA) was used for all statistical analyses. Statistical significance was defined as a p-value of <0.05 (two-tailed).

3.2 A Systematic Review and Meta-Analysis: Medical Futility in In-Hospital Cardiac Arrest Patients

Search strategy and study selection: Peer-reviewed studies were eligible if they comprised either a definition of futility regarding CPR, clinical measures to assess futility, and/or rates of DNR orders in patients for whom CPR attempt was deemed futile. Exclusion criteria were 1) medical futility regarding resuscitation not addressed / population does not include patients in whom futility regarding resuscitation is assessed, 2) patients < 18 years, 3) no clinical peer-reviewed study or conference poster/abstract, or 4) no information on any of the predefined outcome parameters. The digital databases Embase, PubMed, CINAHL and PsycINFO were searched employing a comprehensive search strategy consisting of a combination of subject headings and free-text words. We identified additional studies by screening all references of eligible studies through the cited reference search of Web of Science and PubMed and applied the similar articles search of PubMed.

Outcome measures and data extraction: Outcomes were definitions of futility, measures of futility, and DNR code status in futile patients. Three investigators (H.C., A.V. and K.B.) screened the titles and abstracts of articles with regard to inclusion and exclusion criteria. Two reviewers (H.C. and A.V.) independently assessed the full texts of the remaining studies and disagreements were resolved through discussion with a third reviewer (K.B.). Risk of bias was independently evaluated by two authors (A.V. and K.B.) for every relevant outcome of all included studies and disagreements were resolved by discussion until consensus was found.

Data analysis: We calculated risk ratios (RR) and 95% CI. A fixed-effects model was used to pool data. Heterogeneity was identified through visual inspection of the forest plots and the I^2statistic was used to assess the consequences of heterogeneity on the meta-analysis. Cut-off values for stratification were chosen based on the cut-offs used in the literature (De Vos et al., 1998; Ebell et al., 2013; Ebell et al., 1997; George et al., 1989; Piscator et al., 2018) and risk scores' specificity was calculated separately for each study. If data were not suitable for direct comparison, we applied narrative synthesis. Statistical analyses were conducted using the METAN package in Stata (Stata MP, version 15.1; StataCorp LP), a two-sided $p < .05$ was considered statistically significant.

3.3 A Narrative Review: Reducing Psychological Distress in Resuscitators

Search strategy and study selection: The presented literature is based on a search of terms in scientific databases drawn from a set of key articles and initial keywords such as stress, distress, CPR, cardiopulmonary resuscitation, and performance. Peer-reviewed studies retrieved in scientific databases were eligible.

Outcome measures: We identified a working definition of stress, methods of measuring stress and reviewed existing evidence on the relationship between measures of stress and performance, particularly in emergency situations such as CPR.

Data analysis: Included literature was summarized to the current state of research concerning the influence of stress on resuscitation performance and was narratively presented.

3.4 A Randomized Controlled Trial: Effectively Teaching Breaking Bad News

Study setting and population: 4th year medical students at the University of Basel were asked to participate in the study in December 2019, with 181 students giving informed consent. All students attended a mandatory lecture teaching communication skills in BBN focusing on the BAD scheme (Becker et al., 2019). Students were then randomized 1:1 to either a control or intervention group and stratified by gender to ensure equal gender distribution. Students then participated in an E-learning consisting of two parts. The first part included three teaching videos demonstrating the same physician and patient during a consultation in an acted-out BBN situation in an emotion-focused, information-focused, and patient-centered version. The second part consisted of an examination video in which students were asked to recognize, tag and name specific communication elements and missed opportunities according to the BAD scheme. The intervention group first worked on the teaching videos and was then able to access the examination video. The control group annotated the examination video before gaining access to the teaching videos.

Data collection: Data were collected during the examination videos with student annotations. Further, students were asked to complete a short questionnaire to assess further predictor and outcome variables at the end of the teaching and examination video.

Predictor variables: Predictor variables were student-related factors assessed after the examination video, e.g. sociodemographic and personal experience with a BBN situation, and video-associated factors assessed after each teaching video, e.g. perceived competence, empathy, comprehensibility, and trustworthiness of physician.

Outcome variables: The primary outcome was defined as correctly identified professional utterances and correctly identified missed opportunities. Secondary outcomes were defined as misclassifications, incorrect identifications and identification of BAD elements overall. These variables were gained through independent and, concerning group allocation, blinded ratings of the student annotation by the authors (A.V. and T.U.) following a template according to the BAD scheme. Unclear ratings and disagreements were resolved with a third author (W.L.). Further, secondary outcomes were perceived preparedness for the examination video and self-rating of own performance.

Statistical analysis: We used t-tests to calculate differences and estimated Cohen's d for effect size between the intervention and the control group for the primary and secondary outcomes, as well as for gender differences. Further, we calculated 2x2 ANOVAs for group and gender differences to calculate possible interaction terms. Last, we calculated univariable regression models for video-associated predictors with the three teaching videos. STATA 15.0 was used for all statistical analyses and a two-sided p-value of <.05 was considered significant.

4 Summary of the Results

4.1 Two Prospective Observational Cohort Studies

4.1.1 Prevalence and Risk Factors Associated with Psychological Distress in COVID-19 Patients and Relatives

4.1.1.1 Psychological Distress in COVID-19 Patients and Relatives 30 Days after Hospital Discharge

We conducted telephone interviews with 126 Covid-19 patients and 153 of their relatives. Patients were on average 58 years old, 60.3% were male, and mean duration of hospitalization was 9 days with 15.1% requiring intensive care. Relatives had a mean age of 58 years, 75.2% were female, and 50.3% were patients' spouses

Primary endpoint: Among 126 included patients, 24 (19.1%) met the criteria for psychological distress, i.e., symptoms of depression and/or anxiety. Of those, 22 (17.5%) patients suffered from symptoms of anxiety and 10 (7.9%) of depression. In multivariate logistic regression analyses three factors were independently associated with psychological distress in patients: resilience (OR 0.82; 95%CI 0.71 to 0.94; p = 0.005), high levels of perceived stress (OR 1.21; 95%CI 1.06 to 1.38; p = 0.006) and low frequency of contact with relatives (OR 7.67; 95%CI 1.42 to 41.58; p = 0.018). The model showed good discrimination, with an AUC of 0.92.

Secondary endpoint: Among 153 relatives, 35 (22.9%) displayed clinically relevant psychological distress. Of those, 25 had symptoms of anxiety (16.3%) and 23 had symptoms of depression (15%). For relatives, only two factors remained significantly and independently associated with psychological distress in a final overall model: resilience (OR 0.85; 95%CI 0.75 to 0.96; p = 0.007), and perceived overall burden caused by COVID-19 (OR 1.72; 95%CI 1.31 to 2.25; p<0.001). The overall model showed good discrimination of relatives for psychological distress with an AUC of 0.87.

Further, 10 (8.7%) patients and 3 (2%) relatives showed symptoms of PTSD. Associated risk factors for patients in univariate analyses controlled for age, gender and study center were non-Swiss citizenship (OR 9.83; 95%CI 1.62 to 59.64; p = 0.013), non-central/western European background (OR 15.05: 95%CI 1.3 to 173.21; p = 0.030), and higher worries due to COVID-19 media reports (OR 1.36; 95%CI 1.02 to 1.82; p = 0.039). A multivariate model containing these factors showed good discrimination with an AUC of 0.84 and the factor worries due to COVID-19 media reports remaining independently associated. Due to the low number of events for PTSD in relatives, no regression models were calculated.

4.1.1.2 Psychological Distress in COVID-19 Patients and Relatives 90 Days after Hospital Discharge

We conducted telephone interviews 90 days after hospital discharge with 108 Covid-19 patients and 120 of their relatives. Patients' mean age was 58 years, 41.1% were female, were hospitalized on average for 9 days with 16.8% of patients requiring intensive care. Relatives were on average 58 years old, 79% were female, and 52.1% were patients' spouses.

Primary endpoint: Clinically relevant psychological distress 90 days after hospital discharge was present in 23 patients (21.3%). Of those, 20 (18.5%) displayed symptoms of anxiety and ten (9.3%) symptoms of depression, with seven patients (6.5%) showing both. For patients, risk and protective factors associated with psychological distress included sociodemographic, (i.e., female gender), illness-related, (i.e., lower perceived health status), psychosocial, (i.e., lower resilience, higher level of perceived stress, increased worries due to COVID-19 media reports, worries by isolation measures, burden by boredom, worries about job situation, worries about medical care), and hospital-related factors, (i.e., burden of having no visitors and missing physical contact). A model including these significant factors showed good discrimination, with an AUC of 0.84.

Secondary endpoint: Twenty-two relatives (18.3%) met the criteria for psychological distress 90 days after hospital discharge. Of those, 17 (14.2%) relatives showed symptoms of anxiety and 13 (10.8%) symptoms of depression with eight relatives (6.7%) displaying both. For relatives, relevant risk factors for psychological distress were including illness-related (i.e., lower perceived health status), psychosocial (i.e., lower resilience, higher level of perceived stress, type of communication between relatives and patients, higher perceived overall burden, increased worries due to uncertain prognosis, higher burden of isolation measures, helpfulness of sport, other coping strategies), and hospital-related factors, (i.e., higher burden due to not being able to visit the patient, missing physical closeness). A model including these factors showed good discrimination with an AUC of 0.95.

Concerning PTSD, 8 patients (7.8%) and 8 relatives (7.1%) showed clinically relevant symptoms. Risk factors for PTSD in patients were sociodemographic factors (i.e., female gender, cultural background, civil status), illness-related factors (i.e., lower perceived health status) and psychosocial factors (i.e. higher perceived stress, increased worries due to COVID-19 media reports). For relatives, risk for PTSD was associated with illness-related factors (i.e. lower perceived health status), psychosocial factors (i.e. intake of psychotropic drugs, lower resilience, higher perceived stress, increased worries due to COVID-19 media reports) and hospital-related factors (i.e. higher burden of isolation measures and of not being able to visit the patient).

4.1.2 Prevalence and Risk Factors for Post-Intensive Care Syndrome in Out-of-Hospital Cardiac Arrest Patients

One-hundred thirty-nine (89.1%) patients were reachable at the 3-month follow-up, and 110 (70.5%) at the 12-month follow-up. Ninety-three (59.6%) participants completed both interviews. Patients' median age was 62.8 years old, 17% were female, with a median duration of ICU stay of 4 days and median hospital length of stay of 13 days. Patients suffered from a high burden of comorbidities and cardiovascular risk factors.

Primary endpoint: Sixty-nine patients (49.6%) showed evidence of PICS three months after OHCA. Of those, 36.7% displayed physical impairment, 25.2% cognitive impairment, and 12.9% psychological distress. Several factors were associated with PICS, adjusted for age and gender, including baseline severity of illness scores (APACHE II: OR 1.07, 95%CI 1.02 to 1.12, p=0.007 and SAPS II: OR 1.03, 95%CI 1.01 to 1.06, p=0.006), intubation (OR 2.21, 95%CI 1.02 to 4.78, p=0.043) and duration of intubation (in days) (OR 1.21, 95%CI 1 to 1.46, p=0.046), length of ICU stay (in days) (OR 1.11, 95%CI 1.01 to 1.21, p=0.022), functionality at discharge (poor mRS score: OR 4.35, 95%CI 1.7 to 11.1, p=0.002 and CPC score: OR 3.39, 95%CI 1.46 to 7.88, p=0.005), as well as work loss within the 3-month follow-up (OR 14.53, 95%CI 1.8 to 117.56, p=0.012).

Secondary endpoint: After twelve months, 52 patients (47.3%) showed evidence of PICS with 36.7% displaying physical impairment, 22.2% cognitive impairment, and 12.7% psychological distress. Predictors, adjusted for age and gender, associated with PICS were initial severity of illness scores (APACHE II: OR 1.08, 95%CI 1.02 to 1.14, p=0.008) and functionality at discharge (poor mRS score: OR 3.97, 95%CI 1.42 to 11.12, p=0.009; and CPC score: OR 3.22, 95%CI 1.29 to 8.04, p=0.012). In addition, risk for PICS was lower in patients not needing rehabilitation (OR 0.31, 95%CI 0.12 to 0.82, p=0.019) and in turn increased with longer duration of the rehabilitation (in days) (OR 1.24, 95%CI 1.03 to 1.5, p=0.027). Further, persistence of PICS between 3- and 12-month follow-up was shown with a significant Chi-square test, $X2(1, N=93) = 23.6$, $p<.001$. Inter-correlations between the different domains of PICS at 3-month follow-up further showed significant correlations between the physical and psychological domain and between the physical and cognitive domain, with similar results found after 12 months.

4.2 A Systematic Review and Meta-Analysis: Medical Futility in In-Hospital Cardiac Arrest Patients

Of a total of 1966 studies, after removing duplicates and screening titles, abstracts, and full text articles, 31 studies (Aarons & Beeching, 1991; Barjaktarevic et al., 2015; Becker,

Manzelli, et al., 2021; Bowker & Stewart, 1999; Chevaux et al., 2015; Cohn et al., 1993; Curtis et al., 1995; De Vos, 2001; De Vos et al., 1998; Ebell & Afonso, 2011; Ebell et al., 2013; Ebell et al., 1997; George et al., 1989; Kernerman et al., 1997; Marik & Craft, 1997; Murphy et al., 1989; O'Keeffe & Ebell, 1994; Ohlsson et al., 2016; Ohlsson et al., 2014; Osinski et al., 2017; Oswald, 2008; Piscator et al., 2018; Piscator et al., 2019; Reisfield et al., 2006; Rubins et al., 2019; Saltbaek et al., 2013; Stewart et al., 1996; Teno et al., 1994; Thai & Ebell, 2019; Truog et al., 1992; Yüce et al., 2017) were eligible for inclusion. Of those, 11 studies were included in the meta-analyses.

Definitions of futility*:* Twenty-seven studies included short descriptions or definitions of medical futility for CPR, which varied broadly in content and specificity. Six studies defined futility as a very low likelihood of survival after CPR following cardiac arrest (Becker, Manzelli, et al., 2021; Curtis et al., 1995; Ebell & Afonso, 2011; Ebell et al., 2013; Kernerman et al., 1997; Teno et al., 1994). Nine studies presented risk scores with a cut-off score indicating futility (Becker, Manzelli, et al., 2021; Cohn et al., 1993; George et al., 1989; Stewart et al., 1996), or extremely low chance of survival with favorable neurologic outcome, defined as CPC 1 (Ebell et al., 2013; Rubins et al., 2019; Thai & Ebell, 2019) or 1 to 2 (Piscator et al., 2018; Piscator et al., 2019). Ten studies provided unspecific definitions either based on clinical conditions (e.g., age, metastatic cancer,) or based on an outcome (e.g., “prolonging the patient’s suffering and therefore harming the patient”) (Aarons & Beeching, 1991; Chevaux et al., 2015; Curtis et al., 1995; De Vos, 2001; De Vos et al., 1998; Murphy et al., 1989; Osinski et al., 2017; Oswald, 2008; Reisfield et al., 2006; Saltbaek et al., 2013). Also, several reported specific scenarios in which CPR would be futile (e.g., recurrent cardiac arrest, severe burn injuries) (Barjaktarevic et al., 2015; Marik & Craft, 1997; Truog et al., 1992; Yüce et al., 2017).

DNR code status in patients for whom CPR was deemed futile: Four studies reported how many patients had a DNR code status for whom CPR was deemed futile (Aarons & Beeching, 1991; Becker, Manzelli, et al., 2021; Stewart et al., 1996; Teno et al., 1994). The rates of DNR code status varied considerably between 27% and 71%. Further, considerable variation in the definition of futility was found among the studies.

Meta-analysis of pre-arrest risk scores: The eleven included studies examined several risk scores assessing the pre-arrest risk of death during hospitalization after CPR for IHCA in individual patients (Bowker & Stewart, 1999; Ebell et al., 2013; Ebell et al., 1997; George et al., 1989; O'Keeffe & Ebell, 1994; Ohlsson et al., 2016; Ohlsson et al., 2014; Piscator et al., 2018; Piscator et al., 2019; Rubins et al., 2019; Thai & Ebell, 2019): The Pre-Arrest Morbidity (PAM) index, the Prognosis After Resuscitation (PAR) score, the Good Outcome Following Attempted Resuscitation (GO-FAR) score and the Prediction of Outcome for In-

Hospital Cardiac Arrest (PIHCA) score. Overall, the meta-analysis comprised 118,315 patients.

First, five studies with 1621 patients reported PAM scores and in-hospital mortality (Bowker & Stewart, 1999; Ebell et al., 1997; George et al., 1989; O'Keeffe & Ebell, 1994; Ohlsson et al., 2014). The PAM index was associated with a significantly higher risk of in-hospital death at a cut-off score of PAM>8 (RR 4.10 [95 %CI 1.39–12.11]). Second, four studies with 1481 patients reported PAR scores and mortality (Bowker & Stewart, 1999; Ebell et al., 1997; O'Keeffe & Ebell, 1994; Ohlsson et al., 2014). The PAR score was associated with a significantly higher risk of death until discharge at a cut-off score of PAR > 8 (RR 3.11 [95 %CI 1.59–6.05]). Third, five studies with 114,585 patients reported GO-FAR scores and poor neurologic outcome or in-hospital death (Ebell et al., 2013; Ohlsson et al., 2016; Piscator et al., 2018; Rubins et al., 2019; Thai & Ebell, 2019), in which the GO-FAR score was associated with a significantly higher risk of poor neurologic outcome (CPC<1) and in-hospital death at a cut-off score of ≥14 (RR 6.92 [95 % CI 6.42–7.46]). Last, one study with 628 patients evaluated the PIHCA score and poor neurologic outcome or in-hospital death (Piscator et al., 2019). A very low or low (3% chance of favorable neurological survival) PIHCA score was associated with a significantly higher risk of poor neurologic outcome (CPC<2) and death until discharge (RR 11.46 [95% CI 1.65–79.61]).

4.3 A Narrative Review: Reducing Psychological Distress in Resuscitators

Main findings: Stress has been reported to reduce aspects of general performance, such as narrowing the attention span (Chajut & Algom, 2003) and impairing retrieval of previously learned information in non-stressful conditions (de Quervain et al., 2000; Het et al., 2005), but also to protect performance by enhancing memory and retrieval in affect-laden situations (Buchanan & Lovallo, 2001; Cahill & McGaugh, 1995; Luethi et al., 2008). During resuscitation, we found that resuscitators often experience stress on a biological and psychological level (Dias & Neto, 2016; Harvey et al., 2010; Hayes et al., 2007; Morgan & Westmoreland, 2002; Quilici et al., 2005; Scott et al., 2003). Also, we found some associations of higher self-reported stress, as well as physiological stress, to be associated with lower CPR performance (Hunziker et al., 2011; Hunziker et al., 2013; Krage et al., 2017; Tramer et al., 2018). However, other findings showed that stress during CPR does not always lead to performance impairments (Bjorshol et al., 2011; Geeraerts et al., 2017; Keitel et al., 2011; Muller et al., 2009) and that mostly self-reported but not biological stress measures are associated with poorer performance (Hunziker et al., 2011; Hunziker et al., 2013; Keitel et al., 2011; Krage et al., 2017; Muller et al., 2009). Further, there are many stress reducing interventions (Inzana et al., 1996; LeBlanc, 2009; Saunders et al., 1996), yet to the best of our

knowledge, only one intervention targeting stress reduction during CPR exists (Hunziker et al., 2013).

Gender differences: When considering gender differences, some studies have shown female students to present inferior performance (Amacher et al., 2017) and report higher stress levels during CPR than male students (Ghazali et al., 2018), which was found to be negatively associated with each other (Hunziker et al., 2011) despite having equal medical knowledge (McDonough et al., 2000). Yet, CPR performance in women can be improved with a gender-focused intervention (Hochstrasser et al., 2022).

4.4 A Randomized Controlled Trial: Effectively Teaching Breaking Bad News

***Main findings*:** No significant differences were found between the intervention and control group regarding correct identification of BAD elements, the number of identifications of BAD elements overall, correct identification of missed opportunities, or misclassification of BAD elements. However, the number of incorrectly identified elements was significantly higher in the control group versus the intervention group (M [SD] 3.33 [3.39] versus 2.33 [2.57], $p = 0.037$, $d = 0.33$).

***Gender differences*:** The mean number of all annotated items was significantly higher in women than in men (M [SD] 11.32 [6.05] versus 9.43 [5.39], $p = 0.04$, $d = 0.33$). Also, correctly identified BAD elements (M [SD] 4.16 [2.46] versus 2.96 [2.20], $p < 0.01$, $d = 0.51$) and correctly identified missed opportunities (M [SD] 2.60 [1.77] versus 2.08 [1.44], $p = 0.05$, $d = 0.32$) were rated significantly more often by female than male students. No significant differences were found in misclassified or incorrectly identified items. Further, no significant interactions between group and gender for the primary and secondary outcomes were found.

5 Discussion

A relevant proportion of patients after a critical illness with high prognostic uncertainty and risk for mortality suffer from physical and psychological sequelae long after hospitalization. In this dissertation, this has been found in two different patient groups, i.e., in patients after cardiac arrest and COVID-19 patients. High psychological burden was found to prevail at different timepoints up to twelve months after hospitalization. Further, a high prevalence of psychological distress has not only been found in patients, but also in relatives. This stresses the need for adequate care of patients and their relatives during and after hospitalization for physical and psychological health. Adequate care may be achieved through consideration of different risk factors aiding as early identification tools for physicians, tailored interventions and communication strategies. This will be discussed in the following sections.

5.1 Psychological Distress in COVID-19 Patients and Relatives

We have found in both *Study I and II* that COVID-19 patients and their relatives are similarly affected by psychological sequelae, with prevalences of psychological distress, anxiety, depression, and PTSD symptoms ranging between 18.3%-22.9%, 14.2%-17.5%, 7.9%-15%, and 2%-8.7%, respectively. These prevalences are comparable to other study findings at the time (Wu et al., 2020; Zhang et al., 2020). Further, in both studies patients and relatives were found to suffer from higher rates of psychological distress than the Swiss general population at similar time points of the pandemic (de Quervain, Aerni, Amini, Bentz, Coynel, Gerhards, Fehlmann, et al., 2020; de Quervain, Aerni, Amini, Bentz, Coynel, Gerhards, Freytag, et al., 2020). This emphasizes the need to focus on COVID-19 patients and their relatives, as they seem to be an especially vulnerable group with considerably high rates of clinically relevant psychological distress.

Several sociodemographic, illness-related, psychosocial, and hospital-related factors were associated with psychological distress up to three months after hospitalization. Several risk factors emerged as recurring over both time points in patients and relatives and were partly found to be independently associated with psychological distress and/or PTSD:

First, perceived stress and overall burden were found to be predictive of psychological distress at both time points, a risk factor also found in other studies (de Quervain, Aerni, Amini, Bentz, Coynel, Gerhards, Fehlmann, et al., 2020). This is a relevant finding, as especially overall burden, which was rated from 0 to 10, is a simple and time-efficient measure which could be easily implemented in clinical practice and could help to detect at-risk patients.

Second, a characteristic feature of this patient population was the experienced isolation during hospital stay. Accordingly, we found factors around social connectedness as significant

risk and protective factors for mental health: In *Study I*, we found that daily contact with relatives and perceived social support during isolation were associated with lower psychological distress in patients after one month. In *Study II*, we found that the perceived burden of isolation measures, having no visitors or not being able to visit, and missing physical contact were significantly associated with increased psychological distress in patients and relatives. These findings are in line with studies on previous pandemics reporting adverse psychological effects of isolation and quarantine (Brooks et al., 2020; Dorman-Ilan et al., 2020; Shi et al., 2020). Seeing as contact frequency is potentially modifiable in isolation through the help of newer technology, the medical staff should encourage patients and relatives to more frequent digital contact to potentially reduce psychological distress.

Third, resilience was found to be the strongest protective factor from experiencing anxiety, depression or PTSD and is a recurring finding of both *Study I and II* for both patients and relatives. Resilience has previously been linked to mental health, respectively negatively linked to psychological distress (Hu et al., 2015). Even though it is oftentimes considered a trait, it is potentially modifiable (Blanc et al., 2021). Further, during the pandemic the use of resilient coping mechanisms has been shown to have beneficial effects on mental health (Blanc et al., 2021; Prout et al., 2020). Seeing as general resilience interventions exist with positive impacts on individuals' resilience (Joyce et al., 2018), resilience-improving interventions for COVID-19 patients and relatives should be evaluated.

Risk factors more often found for PTSD symptoms at both time-points were cultural background in patients (i.e. non-Swiss citizenship, non-central/western European background) and higher worries due to COVID-19 media reports in both patients and relatives. Individuals with migration backgrounds have been shown to be at higher risk for mental illness such as PTSD (Close et al., 2016), therefore, this patient group should be carefully considered in clinical practice. Also, consumption of media has been found to increase long-term distress of mass trauma in general and also specifically for the COVID-19 pandemic (Dubey et al., 2020; Neria & Sullivan, 2011; Thompson et al., 2019). Therefore, a reduction of media overconsumption might be beneficial for at-risk individuals.

A follow-up study of the same patient sample of *Study I and II* one year after hospitalization found that still 18% of patients suffered from psychological distress and patients with higher levels of anxiety, depression and perceived stress after one month were more likely to experience psychological distress after one year (Becker, Beck, et al., 2021). Seeing as psychological distress remains rather stable over time, monitoring of at-risk patients and adequate interventions are required. Still, only few interventions exist for COVID-19 patients or their relatives with unclear effectiveness on psychological distress (Borghi et al., 2021; Rossi

Ferrario et al., 2021). Seeing as mental health disorders are associated with increased COVID-19 mortality (Fond et al., 2021), the need for adequate interventions is high.

5.2 Long-Term Impairments in Cardiac Arrest Patients

Survivors of a cardiac arrest suffer from a high prevalence of physical, cognitive and psychological sequelae long after hospitalization, which we found in *Study III* as well as in previous studies (Chin et al., 2022; Israelsson et al., 2017; Schluep et al., 2022). We found that these long-term health impairments are partially modifiable as we identified risk factors before, during and after occurrence of a cardiac arrest.

Study IV concerned risk factors before cardiac arrest, specifically when CPR will most likely not yield positive results and is therefore considered futile. This systematic review found few clear clinical definitions of futility for IHCA that allow feasible implementation in clinical practice. Yet, four objective pre-arrest risk scores were found that may aid in quantitatively defining futility (Schneiderman et al., 1990). In our meta-analyses examining the predictive value of the pre-arrest risk scores for survival to discharge (with good neurologic outcome), especially the GO-FAR and the PIHCA score showed high predictive value. Further, we found a considerable number of patients that would be deemed futile for CPR without a having a DNR order in place, with high variations between studies. Clearer definitions and implementation of good prognostic tools are required which could reduce the amount of futile CPR and in turn, reduce the potential harm of neurological damages or undignified deaths in cardiac arrest patients (Blinderman et al., 2012). Clear definitions and prognostic tools could also aid in patient-centered communication and shared decision-making process by giving patients the opportunity of making informed decisions about their un(wanted) medical care with clear and reliable information (Dowsett et al., 2000; Mast et al., 2005). This in turn may alter code status decisions and needs more research. Presently, a large multicenter randomized controlled trial is being conducted investigating code status discussions and incorporating risk assessment of futility including the GO-FAR score (https://clinicaltrials.gov/ct2/show/NCT03872154).

During CPR, the narrative review *Study V* found that resuscitators often experience stress during CPR (Dias & Neto, 2016; Harvey et al., 2010; Hayes et al., 2007; Morgan & Westmoreland, 2002; Quilici et al., 2005; Scott et al., 2003) and that both subjectively experienced and physiologic stress have been found to lower CPR performance (Hunziker et al., 2011; Hunziker et al., 2013; Krage et al., 2017; Tramer et al., 2018). Important gender differences were found in which female resuscitators experience more stress during CPR which was associated with inferior CPR performance (Amacher et al., 2017; Ghazali et al., 2018; Hunziker et al., 2011). Following, possible stress of resuscitators may have a grave

influence for CPR outcome. Yet, no studies assess long-term outcomes of CPR performance, such as survival to discharge or neurological outcome, therefore not allowing for further conclusions. Further, only one intervention targeting general stress reduction during CPR was found (Hunziker et al., 2013) and one effective gender-focused intervention improving female resuscitators performance (Hochstrasser et al., 2022). Further development and testing of tailored stress reduction interventions for resuscitators is therefore highly needed. Also, as some mechanisms of teamwork have been found to improve performance in stressful situations (Hockey, 1997), team-related factors should be taken into account to possibly enhance CPR performance.

After a cardiac arrest, we found that nearly half of OHCA survivors in our patient cohort suffered from long-term health consequences in *Study III.* One of three patients suffered from physical impairments, one in four from cognitive impairments, and one in eight patients showed clinically relevant psychological distress, with comparable prevalence rates at 3 and 12 months following cardiac arrest. The prevalence of PICS in our cohort is comparable to other ICU cohorts, yet with different distributions among the domains (Marra et al., 2018). We found several clinical and psychosocial factors associated with long-term outcomes. During hospitalization, risk factors such as severity of illness, adrenaline dose given, intubation, and functionality (mRS and CPC score) at discharge were predictive for PICS, several factors which have also previously been found to be associated with adverse outcomes in OHCA patients (Peskine et al., 2021). After hospital discharge, work loss within three months post-discharge and the need for and prolonged rehabilitation were associated risks. Some of these factors may be partly modifiable and are often already implemented in ICU care, such as early weaning strategies to decrease the time of intubation, use of lower sedative drug doses or daily stops of anesthetics to avoid oversedation (Barr et al., 2013; Olsen et al., 2020). Others may be used as screening tools to identify high-risk patients. For instance, the mRS and CPC score are two quickly assessable cognitive functionality scores, which could be easily implemented to assess high-risk patients as early as at hospital discharge. Further, during rehabilitation screening for PICS could help identify patients needing more medical and psychological support. Still, more research is needed on this topic to allow for more definite conclusions.

5.3 Communication Skills for Professional Patient-Physician Interaction

To effectively communicate such far-reaching medical information as previously discussed, professional communication skills are needed. Concerning the delivery of bad news, we found in *Study VI* that an E-learning assignment could improve medical students' accurate recognition of BBN communication techniques, as students who worked through the

teaching videos were significantly less prone to incorrectly identifying communication elements of bad news. This is a relevant finding, as BBN communication strategies explicitly focus on only giving the most essential information and solely offering more information if requested in order to give the patient enough time to process the bad news (Baile et al., 2000; Becker et al., 2019).

We found gender differences independent of the intervention, with female students identifying more communication elements overall, and correctly identifying more BAD elements and missed opportunities compared to male students. It is unclear if this is due to gender differences concerning higher female adherence to standardized examinations and evidence-based guideline recommendations (Dahrouge et al., 2016) or possibly the tendency of female physicians toward patient-centered care (Roter & Hall, 2004; Stiefel et al., 2013). Nevertheless, our results suggest taking gender-specific differences into consideration for future patient-centered communication training.

Only few other differences in the identification of communication techniques were found between the intervention and the control group. This may be due to a possible ceiling effect resulting from the high training standard of the student sample, which have already undergone a longitudinal training in professional communication with lectures, practice with simulated and real patients as well as E-learning tools throughout their medical education (Kiessling & Langewitz, 2013). Also, the transfer from the learning videos to the examination videos may have been impeded by the use of prototypical situations in the learning videos and an ordinary communication example in the examination video. As erroneous video-based examples have been shown to foster better communication skills in previous studies (Schmitz et al., 2017), possibly incorporating more erroneous, and therefore ordinary communication examples in the teaching videos may help the learning transfer.

The influence of communication strategies on psychological well-being of patients and relatives cannot be concluded by this trial. However, many studies speak for this association (Abazari et al., 2019; Fallowfield & Jenkins, 2004; Roberts et al., 1994) and could be evaluated more specifically in terms of the BAD-strategy and the proposed E-learning tool.

5.4 Strengths and Limitations

Several strengths and limitations of this dissertation must be discussed. A strength is the use of several different methodological approaches with two prospective observational cohort studies, a systematic review, a narrative review and a randomized controlled trial. This allows for a more complex understanding of the understudied topics.

A limitation of this dissertation comprises the many exploratory studies due to few preceding studies in the concerning fields. In *Studies I and II*, COVID-19 as a new infectious

disease presented little scientific knowledge at the beginning of the pandemic and at the time of the trial. Similarly in *Study III*, PICS is a syndrome complex that, even though being more frequently observed in ICU care, is not yet an official diagnosis and lacks clear-cut definitions. Additionally, to the best of our knowledge, no other study has assessed PICS in OHCA patients. Therefore, we opted for extensive and hypothesis-generating studies setting out to maximize knowledge gain. Also, observational studies are hypothesis generating and need interventional studies to conclude for causal effects. Further, sample sizes in the prospective observational cohort studies *Study I, II, III* were limited which decreases the power of the studies.

Concerning the literature reviews, medical futility is a delicate ethical topic which therefore calls for having a carefully thought-out and clear definition. At the same time, few definitions on medical futility for IHCA patients exist, limiting informed research on this topic and the scope of *Study IV*. In *Study V* on the influence of stress on CPR performance, many of the research findings are based on simulation studies and focus on less-experienced personnel, such as residents or medical students. It remains unclear to what extent these findings apply to naturalistic settings and more experienced medical staff. Further, a narrative review is limited in estimating a potential bias in published studies in the studied field.

Also, concerning *Study VI* on E-learning tool for breaking bad news, this trial does not directly conclude on students' communication skills as a behavioral skill, as student annotations in the E-learning do not measure behavior change and therefore limits generalizability on future physician-patient interactions. A test of behavior change in a face-to-face interaction is necessary to clarify this matter. Further, the use of more complex, and therefore reality-based, instead of prototypical video examples as learning videos could help the transfer to real-life situations and should be evaluated in a future trial.

5.5 Conclusion and Future Research

This thesis incorporates much foundational research. This opens the way for well-informed future interventions in the fields of cardiac arrest, COVID-19 and professional patient-physician communication.

In the field of COVID-19, around one quarter of hospitalized COVID-19 patients and their relatives suffer from clinically relevant psychological distress at one and three months after hospitalization. Further, especially several psychosocial and isolation-related risk factors were associated with adverse outcomes which can be used either for early identification of risk patients or modified treatment for prevention of psychological distress. For instance, identification of at-risk patients and relatives in clinical practice may be achievable through especially discriminative factors, such as subjective overall burden, which can be easily and

time-efficiently assessed during hospitalization. Further, due to resilience and social connectedness being recurring protective factors in COVID-19 patients, intervention programs targeting these factors should be developed and tested as a preventative strategy to reduce psychological burden.

Concerning the field of cardiac arrest, possible preventative measures could be implemented and assessed at different timepoints as nearly half of all OHCA survivors suffer from long-term impairments. Two recently developed pre-cardiac arrest risk scores with good discriminative predictive value concerning mortality and neurological outcome in case of a cardiac arrest, the GO-FAR and PIHCA score, may assist in objective code status discussions for physicians and patients and give patients the opportunity of making informed decisions about their un(wanted) medical care. During cardiac arrest, since experienced stress of resuscitators has been shown to have negative effects on CPR performance (Hunziker et al., 2011; Hunziker et al., 2013; Krage et al., 2017; Tramer et al., 2018) and only one intervention targeting stress reduction for resuscitators was identified (Hunziker et al., 2013), more research should examine stress-reducing interventions and its effect on CPR performance. After cardiac arrest, several identified risk factors can be used to predict outcome and guide for either therapeutic management or early identification of a potentially poor outcome despite resuscitation measures. Yet, more knowledge on potential risk factors and their prognostic value for long term impairments such as PICS are needed to draw specific guidelines on how to implement these factors in the management of clinical practice.

Concerning BBN, an E-learning is an easily implementable, low-threshold possibility to advance communication training of medical students or junior physicians. In combination with blended learning, a broad dissemination in medical curricula may be worthwhile. As a next step, the effects of the E-learning should be tested in a face-to-face interaction to test for behavioral changes in communication skills, and, when thoroughly validated, implemented to potentially reduce psychological distress in patients and relatives receiving bad news.

In conclusion, illness and hospitalization do not only entail physical impairments but also psychological distress in a relevant proportion of critically ill patients long after hospital discharge. However, during hospitalization there are risk and protective factors which can help preventatively target at-risk patients for developing psychological sequelae by giving these patients the treatment they need. Furthermore, appropriate communication of bad news and risk communication is of vital importance and can only succeed via professional communication strategies and clearly defined risk factors to be able to reduce potential uncertainty and distress during medical treatment.

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Appendix A

Study I

Beck, K.*, Vincent, A.*, Becker, C.*, Keller, A., Cam, H., Schaefert, R., Reinhardt, T., Sutter, R., Tisljar, K., Bassetti, S., Schuetz, P., & Hunziker, S. (2021). Prevalence and factors associated with psychological burden in COVID-19 patients and their relatives: A prospective observational cohort study. *PLoS ONE, 16*(5), e0250590. https://doi.org/10.1371/journal.pone.0250590

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RESEARCH ARTICLE

Prevalence and factors associated with psychological burden in COVID-19 patients and their relatives: A prospective observational cohort study

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Abstract

Background

Due to the dramatic measures accompanying isolation and the general uncertainty and fear associated with COVID-19, patients and relatives may be at high risk for adverse psychological outcomes. Until now there has been limited research focusing on the prevalence of psychological distress and associated factors in COVID-19 patients and their relatives. The objective of our study was to assess psychological distress in COVID-19 patients and their relatives 30 days after hospital discharge.

Methods

In this prospective observational cohort study at two Swiss tertiary-care hospitals we included consecutive adult patients hospitalized between March and June 2020 for a proven COVID-19 and their relatives. Psychological distress was defined as symptoms of anxiety and/or depression measured with the Hospital Anxiety and Depression Scale (HADS), i.e., a score of $\geq$8 on the depression and/or anxiety subscale. We further evaluated symptoms of post-traumatic stress disorder (PTSD), defined as a score of $\geq$1.5 on the Impact of Event Scale-Revised (IES-R).

Results

Among 126 included patients, 24 (19.1%) had psychological distress and 10 (8.7%) had symptoms of PTSD 30 days after hospital discharge. In multivariate logistic regression

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analyses three factors were independently associated with psychological distress in patients: resilience (OR 0.82; 95%CI 0.71 to 0.94; p = 0.005), high levels of perceived stress (OR 1.21; 95%CI 1.06 to 1.38; p = 0.006) and low frequency of contact with relatives (OR 7.67; 95%CI 1.42 to 41.58; p = 0.018). The model showed good discrimination, with an area under the receiver-operating characteristic curve (AUC) of 0.92. Among 153 relatives, 35 (22.9%) showed symptoms of psychological distress, and 3 (2%) of PTSD. For relatives, resilience was negatively associated (OR 0.85; 95%CI 0.75 to 0.96; p = 0.007), whereas perceived overall burden caused by COVID-19 was positively associated with psychological distress (OR 1.72; 95%CI 1.31 to 2.25; p<0.001). The overall model also had good discrimination, with an AUC of 0.87.

Conclusion

A relevant number of COVID-19 patients as well as their relatives exhibited psychological distress 30 days after hospital discharge. These results might aid in development of strategies to prevent psychological distress in COVID-19 patients and their relatives.

Introduction

In December 2019, a novel Coronavirus causing the Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, leading to a global pandemic. The clinical symptoms of COVID-19 range from mild flu-like symptoms to acute respiratory distress syndrome [1, 2]. While children and healthy young adults are often less affected by the disease, vulnerable individuals such as the elderly and people with chronic lung disease or cardiovascular comorbidities are at high risk of experiencing complicated courses needing invasive ventilation or circulatory support [3, 4].

Recent studies suggest that COVID-19 causes a relevant increase in risks of mortality and morbidity [5–7]. Although the true impact of COVID-19 on mortality and morbidity has become more evident in recent studies, insights regarding psychological burden beyond the acute phase of the illness in these patients and their relatives who may be at high risk for adverse psychological outcomes is limited [8–11]. In fact, most countries, including Switzerland, have implemented orders to isolate at home or other quarantine measures to contain the spread of COVID-19. As a consequence, patients hospitalized for COVID-19 are often quarantined, and visits—also by family members—are limited to prevent further spread of the virus. Research during previous epidemics showed that these may be associated with adverse psychological effects on patients and relatives, including an increased risk of anxiety disorders, depression and post-traumatic stress disorder [PTSD; 8, 11, 12, 13–17]. Research on the short-term psychological consequences of the COVID-19 pandemic has shown adverse psychological effects [18–20]. For instance, a large Swiss survey including 10472 participants of the general public found the prevalence of moderately severe or severe depressive symptoms to increase from 9.1% during confinement at the time of the first pandemic wave to 11.7% during the following partial confinement, and 18% during the second wave [21, 22]. When asked about their symptom levels before the pandemic, i.e., during the first two weeks of February 2020, only 3.4% of participants reported moderately severe or severe depressive symptoms. A cross-sectional German study evaluating 15037 participants from the general population during the beginning of the pandemic reported rates of depressive and anxiety symptoms of

14.3% and 19.7%, respectively [23]. Retrospectively assessed rates of depressive and anxiety symptoms before the pandemic were significantly lower with rates of 7.6% and 9%, respectively. While including large samples, interpretation of findings of these studies is partially limited due to their naturalistic approach and lack of pre-COVID-19 data. Findings of prospective studies assessing probability samples of the general population yielded mixed results. Two prospective studies analyzing the prevalence of anxiety [24] and depression [24, 25] before and after the outbreak in two different samples of the general population each, found an increase in clinically relevant symptoms. Contrary, a Dutch long-term study assessing prevalence of moderate to high levels of anxiety or depression in the general population in November 2019 and March 2020 did not show an increase with rates being 16.9% and 17.0%, respectively [26] and a later follow-up assessment in June 2020 even revealed a significant decrease to 15.3% [27]. Findings of a similar Dutch long-term study in older adults and a study comparing serious psychological distress in two samples of the US general population were in line with this [28, 29].

Insight regarding psychological distress of patients with COVID-19 is limited, so far. A meta-analysis including 50 mostly Chinese studies on the general population, healthcare workers and patients with COVID-19 showed a pooled prevalence of 44% with psychological morbidities [9]. Four of the included studies had assessed patients with COVID-19, yielding a pooled prevalence of 42% for depression, 37% for anxiety disorders and 96% for post-traumatic stress symptoms. The findings regarding depression and anxiety are in line with other meta-analyses and systematic reviews on various populations, few of them patient samples, affected by the COVID-19 pandemic [10, 30] and more recent studies on hospitalized patients. Regarding post-traumatic stress symptoms, a meta-analysis including more recent studies than the meta-analysis of Krishnamoorthy et al. [9] yielded a pooled prevalence of 24% of post-traumatic stress symptoms [31]. Still, studies on samples of the general population included in these systematic reviews and meta-analyses should be viewed with caution due to methodological issues including low representativeness and other sources of bias.

Relatives of patients hospitalized with COVID-19 might be equally affected but evidence is scarce. The study of Dorman-Ilan et al. [32] suggests that both isolated COVID-19 patients and relatives might suffer from similarly high levels of anxiety and depressive symptoms during the initial stage of hospitalization.

While heightened psychological distress during the acute phase of the illness in patients and their relatives can be expected, it might be additionally relevant to investigate how many experience clinically relevant symptoms persisting beyond that initial phase and which characteristics might be related to this. However, only few studies evaluated this, so far. Recent studies from Italy, Turkey and China investigating COVID-19 survivors about one to two months after hospital discharge found a prevalence of 10% to 42% for anxiety [33–35], 11% to 31% for depression [33–35], 12% to 28% for PTSD [33, 35, 36], and 40% for insomnia [33], suggesting persisting psychological distress in a considerable number of patients. Furthermore, a recent Chinese study revealed that 23% of patients still experienced anxiety or depression even 6 months after discharge [37].

Factors associated with increased psychological distress might include sociodemographic, illness-related, psychosocial and hospital-related characteristics [8, 11]. A systematic review on the psychological impact of past viral respiratory epidemics indicated that female patients and those with lower education levels experience increased anxiety, depression and PTSD [8]. Studies evaluating psychological distress in the context of COVID-19 found female gender [32, 37–40], higher age [39, 40], lower education level [39] and not being employed [40] to be associated with anxiety. Further, female gender [37, 38, 40], lower education [18, 35], not being employed [40] and living with children [35] were potential risk factors for depression.

Regarding symptoms of PTSD, female gender [36, 41], younger age [41] and not being employed [36] emerged as potential risk factors. Also, previous research shows that people who follow disaster media closely have higher levels of post-traumatic stress symptoms and psychological distress [42].

Similar to studies on clinical conditions such as traffic accidents [43], stroke [44] or cardiac arrest [45, 46] which found considerable rates of PTSD symptoms, anxiety and depression, psychological distress in COVID-19 patients and relatives might be related to the potentially life-threatening illness requiring hospitalization or critical care and uncertainty about the course or outcome [11, 47–49]. In line with this, duration of hospitalization [40], higher disease severity [35, 37] and ICU stay [11, 50] might be associated with increased psychological distress.

A recent review on the effects of quarantine measures during past outbreaks suggests a negative impact on psychological well-being of patients as well as their relatives especially due to separation from partners and relatives [12]. However, these findings are difficult to transfer as previous outbreaks were either localized or limited in time and by far did not reach the extent of the current COVID-19 pandemic. Studies during the COVID-19 pandemic found perceived stigmatization and feeling isolated with inadequate social support to be associated with increased anxiety, depression and symptoms of PTSD [18, 35, 36]. Lockdown measures may also lead to financial and occupational concerns and contribute to psychological distress [18, 41, 51]. A large study evaluated the association of internal coping mechanisms for emotion regulation with anxiety, depression and symptoms of PTSD applying a machine learning model in 2787 individuals of the general population. Low use of adaptive defense mechanisms, e.g., humor and self-assertion to regulate one's emotions was associated with heightened levels of anxiety, depression and symptoms of PTSD [39]. In the context of potentially protective coping mechanisms, resilience, often defined as the ability to successfully cope with adverse life events, might also be related to psychological distress [52] and is potentially modifiable [53]. A meta-analysis including longitudinal as well as cross-sectional studies evaluating correlations between resilience and mental health showed that resilience is negatively correlated to negative indicators of mental health, such as depression, anxiety and negative affect, and positively correlated to positive indicators of mental health, such as life satisfaction and positive affect [52]. Further, a review on the role of resilience as a protective factor regarding anxiety, depression and post-traumatic stress during the COVID-19 pandemic revealed that "resilient" coping strategies to deal with COVID-19-related distress are common [53]. However, evidence on the nature of the association of resilience and psychological distress is still inconclusive [54–56] and more research is needed to identify effective interventions [53]. Dorman-Ilan et al. [32] found that relatives who did not feel protected by the hospital might suffer from increased anxiety even one month after patients' discharge.

Though there is growing evidence on acute psychological distress in the context of COVID-19, evidence on prevalence and factors associated with persisting psychological distress in patients and their relatives is scarce. Herein, our aim was to assess in parallel the prevalence of and factors associated with persisting psychological burden in COVID-19 patients and their relatives one month after hospital discharge. Such insights may help to prevent these adverse outcomes by focusing on modifiable risk factors and identifying specific treatments to support patients and relatives in the near future.

Materials and methods

Study setting

We conducted this prospective observational cohort study at two tertiary care hospitals in Switzerland—the University Hospital Basel and the Kantonsspital Aarau—from March until

June 2020. The study was approved by the local Ethics Committee (Ethics Committee Northwest and Central Switzerland EKNZ, approval reference number: 2019–01162). All participating patients and relatives provided written informed consent. This manuscript adheres to the STROBE statement [57; see S1 File].

Study population

We screened all consecutively admitted COVID-19 patients and their closest relatives upon hospitalization regarding inclusion and exclusion criteria. COVID-19 was confirmed by reverse transcriptase polymerase chain reaction from nasopharyngeal swabs [45, 58]. Relatives were chosen according to surrogate decision-making rank (spouse > parents/adult children > others) as indicated in patients' medical records. Exclusion criteria for patients and relatives were insufficient knowledge of the local language (German), cognitive impairment, i.e., a condition where patients were not able to understand and respond to the questions of our interview including dementia, delirium and others, or serious psychiatric conditions, e.g., psychosis. Relatives who were subsequently hospitalized due to COVID-19 were included in the patient sample only. There were no exclusions based on patient characteristics and severity or duration of COVID-19 disease. We contacted relatives during hospitalization and patients about one month after hospital discharge by phone and invited them to participate in our study. Those who had agreed received a letter including the study information and informed consent form which they were asked to sign and return. Relatives and patients were excluded if no informed consent was provided.

Collection of potential predictor and outcome variables of patients and relatives

In this prospective observational cohort study, we conducted telephone interviews with all participating patients and relatives one month after hospital discharge to collect data on potential risk and protective factors concerning the time of hospitalization as well as on psychological outcome at the time of the assessment. For patients we additionally reviewed their medical charts to obtain relevant medical information. For relatives of patients that were hospitalized during the study period, we did a baseline interview upon admission of the patient. Several predictor variables specific to COVID-19 were assessed by items specifically designed for the purpose of this study. For the assessment of the other factors, we used well-established clinical risk scores and validated psychometric measures. We assessed potential predictor variables from four domains, i.e., sociodemographic, illness-related, psychosocial and hospital-related factors. While items in the sociodemographic domain were the same for both patients and relatives, factors in the other three domains partially differed to account for patient- and relative-specific characteristics (see Tables 2 and 3).

Variables collected upon hospitalization

Sociodemographic factors were assessed for patients and relatives and included age, gender, citizenship, cultural background, religious affiliation, civil status, children and current job situation.

Illness-related factors. For patients, in the domain of illness-related factors we assessed variables such as timepoint of COVID-19 diagnosis, duration of hospitalization, antibiotics during hospitalization, investigational therapy, anxiolytics during hospitalization, ICU stay, and intubation. Based on patients' medical condition at the end of their hospitalization for COVID-19, we calculated the Charlson Comorbidity Index (CCI) [59], a score which characterizes the severity of comorbidity and predicts ten-year mortality. Further, we collected

patients' vital signs and calculated the National Early Warning Score (NEWS) [60], a commonly used tool that assesses the severity of a patient's illness and detects patients prone to clinical deterioration.

For relatives, the domain of illness-related factors included items assessing if the relative was quarantined or infected with SARS CoV-2, the time point of the patient's COVID-19 diagnosis, and if the patient had died due to COVID-19.

Psychosocial factors. For relatives, the relationship with patient and whether they lived in the same household as the patients was assessed.

Variables collected at 30 days after hospital discharge

Illness-related factors. Self-perceived overall health status was assessed using the visual analogue scale (VAS) of the EuroQol, ranging from 0 (worst imaginable health) to 100 (best imaginable health) at 30-day follow-up for patients and relatives [61, 62].

Psychosocial factors. For both patients and relatives, psychosocial factors were assessed, such as pre-existing psychological comorbidities, and intake of psychotropic drugs, the amount of COVID-19 media consumption and worries due to COVID-19 media reports (on a VAS 0–10), the frequency of contact between patients and relatives, as well as type of communication. Patients' and relatives' pre-existing psychological comorbidities were inquired during the telephone interview by asking participants directly if psychological comorbidities had been diagnosed previously, e.g., depression, anxiety disorder as well as through questions about psychotherapeutic or pharmaceutic treatment, e.g., antidepressants. In patients, we additionally reviewed medical charts regarding information on pre-existing psychological comorbidities. Further, items designed for the purpose of this study were assessed, such as current worries or burdens and helpfulness of different coping strategies, all rated on a VAS 0–10.

Also, we evaluated perceived stress of patients and relatives with the Perceived Stress Scale (10-item version; PSS-10; Cronbach's alphas $\geq$0.80), a well-established self-report measure assessing how unpredictable, uncontrollable and overloaded respondents perceived their life during the last month [63, 64]. Further, we estimated resilience of patients and relatives using the 10-item version of the Connor-Davidson Resilience Scale (CD-RISC-10), which refers to the preceding month and assesses characteristics of resilience that can also be framed as stress-coping ability [65]. The CD-RISC is widely applied in clinical research and the original 25-item questionnaire as well as the 10-item version showed good validity with a Cronbach's alpha of 0.89 and 0.88 as well as 0.94, respectively [55, 65, 66]. Further, the CD-RISC showed high test-retest reliability over a 12-month follow-up period [67–69]. Cronbach's alpha was 0.86 in our patient sample and 0.76 in our relative sample.

Hospital-related factors. We assessed several hospital-related factors through items specifically designed for this study. Patients and relatives were asked whether the hospital's psychosocial care team was involved, the burden of having no visitors or not being able to visit (VAS 0–10) and missing physical closeness of their relatives (VAS 0–10).

Patients were further asked whether there was contradictory information, i.e., information from one treating team member did not match information from other treating team members, they received by the medical team (VAS 0–10) and the perceived competence of the treating physician (VAS 0–10).

Relatives were asked whether they were in contact with the medical team, the satisfaction with the communication with the medical team (VAS 0–10), whether they received information regarding the patient's prognosis, whether patient's medical care was perceived as sufficient or inadequate, the comprehensibility of medical information (VAS 0–10) and whether they received recommendations regarding own care.

Outcome variables

Psychological distress. All outcome variables were collected 30 days after hospital discharge. Psychological distress, i.e., symptoms of anxiety and/or depression experienced by patients and relatives, was measured by the Hospital Anxiety and Depression Scale [HADS; 70]. Cronbach's alpha was ≥0.80 for both the anxiety and depression subscale in both the patient and relative sample. In line with previous research, we used a cut-off value of ≥8, indicating moderately severe symptoms, and operationalized presence of psychological distress as a score of ≥8 (range: 0 to 21) on either the depression or the anxiety subscale of the HADS [70, 71]. The questionnaire was specifically developed for patients with physical disease and intentionally excludes items associated with physical symptoms to avoid confounding with psychopathological symptoms [70]. Good reliability and validity were shown for the HADS, with a Cronbach's alpha of 0.83 and 0.82 for the subscales anxiety and depression, respectively, and an optimal balance between sensitivity and specificity of approximately 0.80 when applying a cut-off score of ≥8 on both subscales [71].

Symptoms of post-traumatic stress disorder. Further, symptoms of post-traumatic stress disorder were assessed through a German translation of the Impact of Event Scale-revised [IES-r; 72–74] which had a Cronbach's alpha of ≥0.90 in both our patient and relative sample. The IES-r is a 22-item questionnaire which assesses symptoms of emotional distress caused by traumatic events and is divided into three subscales, i.e., intrusion, avoidance and hyperarousal. It is also applicable in general population samples and has been shown to have high internal consistency with a Cronbach's alpha of 0.96 and good diagnostic accuracy when applying a cut-off score of 1.5 [75].

Statistical analyses

Descriptive statistics, i.e., frequencies as well as means and standard deviations were used to display characteristics of the patient and relative sample. We stratified the two samples based on the psychological distress whereas a score of ≥8 on the anxiety and/or depression scale of the HADS was determined as presence of psychological distress and a score of <8 on both scales as absence of psychological distress.

We conducted all analyses separately for each the patient and the relative sample. We evaluated associations between potential predictors and outcomes, separately in two steps, through univariate and multivariate analyses. To account for missing data in predictors used in the multivariate analyses, we imputed datasets using multiple imputations by chained equations. Imputations were calculated using multiple covariables within domains also including main outcomes to reduce bias as previously suggested [76], i.e. for patients: age, gender, children, duration of hospitalization, Charlson Comorbidity Score, NEWS score, ICU stay, pre-existing psychological diagnoses, worries due to COVID-19 media reports, worries about uncertain prognosis, burden of isolation measures, worries about health of relatives, helpfulness of social contacts, helpfulness of distraction, CD-RISC-10, PSS-10, involvement of psychosocial care team, burden of having no visitors, missing physical closeness, and psychological distress (HADS); for relatives: age, gender, cultural background, religion, civil status, children, current job situation, relationship with patient, EuroQol VAS, pre-existing psychological diagnoses, psychotropic drugs, CD-RISC-10, PSS-10, worries due to COVID-19 media reports, worries about infection, worries about uncertain prognosis, contact with medical team, burden of having no visitors, missing physical closeness, and psychological distress (HADS). Model performance of imputed data was also compared to those of crude values to check consistency. We found a similar pattern when doing a full set analysis (see S1 and S2 Tables in S1 File).

First, we calculated univariate logistic regression models separately for patients and relatives. We further investigated the associations between each variable and psychological burden by adjusting each of these analyses for age, gender and study center. In a next step, we calculated a separate multivariate logistic regression model for each domain, resulting in four models in each sample. Each of these models included predefined factors from the respective domain, i.e., a) age for the sociodemographic model, b) duration of hospitalization, use of anxiolytics during hospitalization, and ICU stay for the illness-related factors model, c) burden of isolation measures due to COVID-19 and coping through social contacts in the psychosocial model, and d) burden of having no visitors and missing physical closeness in the hospital-related factors model. In addition, we included all factors that were significantly associated with psychological distress in the previous, age-, gender- and study center-adjusted analyses for each domain. Third, to evaluate which factors might be independently associated with psychological distress, we analyzed an overall model containing all factors that were significantly associated with psychological distress within the four domain models. We calculated odds ratios (OR) and 95% confidence intervals (CI). A p-value of $< .05$ (two-tailed) was considered significant. Areas under the curve (AUC) were created to evaluate the potential prognostic value of the factors regarding psychological distress. All statistical analyses were conducted using Stata 15 (Stata Corp, College Station, Texas, USA).

Results

Characteristics of the study sample

Between March and June 2020, a total of 301 patients with COVID-19 were hospitalized in the University Hospital Basel (n = 198) and the Kantonsspital Aarau (n = 103) (Fig 1). Forty of these patients (13.3%) died during hospitalization or within 30 days after discharge, 54 (17.9%) were unable to speak the local language (German), 32 (16.6%) met exclusion criteria such as

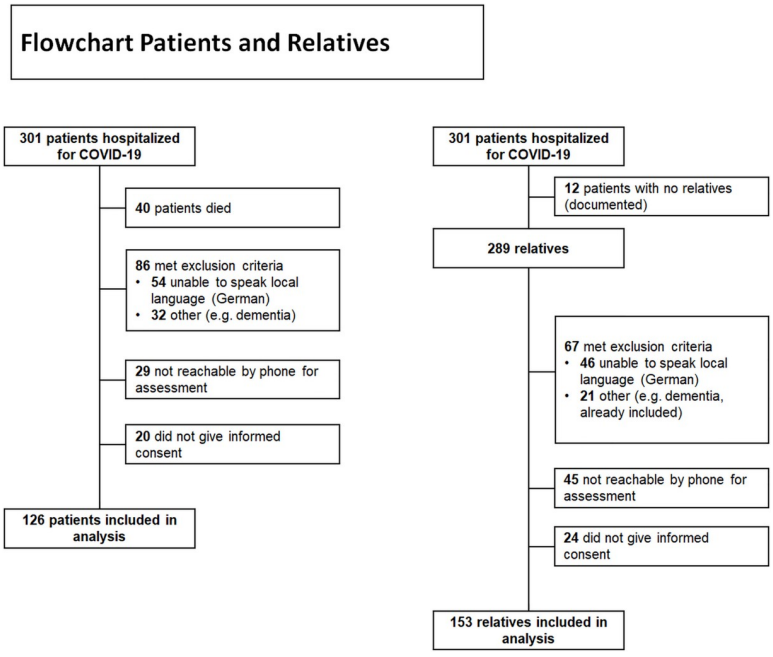

Fig 1. Flow diagram of the study population. Legend: Flow diagram illustrating inclusion and exclusion of eligible participants.

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Table 1. Sociodemographic and clinical characteristics the study populations.

Sociodemographic and clinical characteristics		Patients	Relatives
n		126	153
Age (years)		58.2 (16.35)	57.7 (14.94)
Gender (female)		50 (39.7%)	115 (75.2%)
Citizenship	Switzerland	86 (68.3%)	125 (81.7%)
	Germany	14 (11.1%)	7 (4.6%)
	France	5 (4.0%)	6 (3.9%)
	Other	21 (16.7%)	16 (10.5%)
Cultural background	Central Europe	89 (70.6%)	113 (73.9%)
	Western Europe	11 (8.7%)	8 (5.2%)
	Southern Europe	16 (12.7%)	18 (11.8%)
	Northern Europe	2 (1.6%)	5 (3.3%)
	Asia	4 (3.2%)	4 (2.6%)
	Other	4 (3.2%)	5 (3.3%)
Religious affiliation	Catholic	33 (26.4%)	46 (30.3%)
	Protestant	32 (25.6%)	48 (31.6%)
	Other Christian denomination	9 (7.2%)	10 (6.6%)
	Jewish	2 (1.6%)	2 (1.3%)
	Muslim	11 (8.8%)	8 (5.3%)
	Other religion	3 (2.4%)	3 (2.0%)
	No religious affiliation	35 (28.0%)	35 (23.0%)
Civil status	Married/in partnership	80 (63.5%)	110 (72.4%)
	Divorced	22 (17.5%)	14 (9.2%)
	Widowed	9 (7.1%)	12 (7.9%)
	Single	15 (11.9%)	16 (10.5%)
Children, yes		86 (70.5%)	114 (74.5%)
Education	High School	13 (10.7%)	7 (4.6%)
	Apprenticeship	83 (68.6%)	99 (65.6%)
	College/University	25 (20.7%)	45 (29.8%)
Current job situation	Employed	72 (57.6%)	81 (53.3%)
	Unemployed	1 (0.8%)	4 (2.6%)
	Retired	42 (33.6%)	56 (36.8%)
	Disability benefits	6 (4.8%)	3 (2.0%)
	Homemaker	2 (1.6%)	7 (4.6%)
	Other	2 (1.6%)	1 (0.7%)
Previous psychological therapy		7 (5.7%)	7 (4.7%)
Pre-existing psychological comorbidities		18 (14.8%)	18 (12.1%)
Patient characteristics			
Duration of hospitalization (days), mean (SD)		9.00 (6.49)	
Severity of illness (NEWS score), mean (SD)		6.21 (3.71)	
Comorbidity (CCI), mean (SD)		2.40 (2.17)	
Antibiotics during hospitalization		39 (31.2%)	
Oxygen supply	No oxygen supply	49 (38.9%)	
	Nasal cannula/NIV	65 (51.6%)	
	Intubation	12 (9.5%)	
Anxiolytics during hospitalization		21 (16.9%)	
Investigational treatment[a]		85 (68.0%)	
ICU stay (yes/no)		19 (15.1%)	

(*Continued*)

Table 1. (Continued)

Sociodemographic and clinical characteristics		Patients	Relatives
Relative characteristics			
Relationship to patient	Patient is partner		77 (50.3%)
	Patient is child		12 (7.8%)
	Patient is sibling		15 (9.8%)
	Patient is parent		37 (24.2%)
	Other		12 (7.8%)
Relative living in same household with patient			83 (54.2%)
Patient died (bereaved relatives)			26 (17%)
Relative quarantined			64 (48.5%)
Relative also infected with COVID-19			51 (34.5%)

Data are presented as n (%) or mean (standard deviation).

Abbreviations: SD, standard deviation; NEWS, National Early Warning Score; NIV, Non-invasive ventilation; ICU, Intensive Care Unit; CCI, Charlson Comorbidity Index

[a] Investigational treatment: Hydroxychloroquine, Lopinavir/Ritonavir, Remdesivir, Tocilizumab, Convalescent Plasma

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dementia or severe underlying psychiatric conditions, 29 (9.6%) were not reachable by phone for assessment, and 20 (6.6%) did not give informed consent. In 12 (4%) of all 301 hospitalized patients no relatives were documented in the medical charts. As we identified and approached only one relative per patient, there were therefore 289 potentially eligible relatives left. Of these 289 relatives, 15.9% did not speak German and 7% were excluded due to other criteria, e.g., cognitive impairment or being already included in the patient sample. Forty-five (15.6%) were not reachable by phone and 24 (8.3%) did not give informed consent. Thus, the final cohort consisted of 126 patients and 153 relatives. Table 1 shows sociodemographic and clinical characteristics of the participants.

Psychological distress in patients 30 days after discharge

Twenty-four patients (19.1%) showed psychological distress, i.e., symptoms of depression and/or anxiety. Of those, 22 (17.5%) patients showed symptoms of anxiety and 10 (7.9%) showed symptoms of depression.

Table 2A and 2B give a detailed overview of the associations with psychological distress for patients.

Factors associated with psychological distress in patients. Several factors were associated with psychological distress in univariate models, including sociodemographic factors, i.e., patient gender, religious affiliation, illness-related factors, i.e., self-perceived overall health status, psychosocial factors, i.e., pre-existing psychological comorbidities, resilience, perceived stress, worries due to COVID-19 media reports, frequency of contact with relatives, worries about uncertain prognosis, burden of isolation measures due to COVID-19, worries about health of relatives, and hospital-related factors, i.e., burden of having no visitors. All these variables except from burden of isolation measures and having no visitors were still significantly associated when these analyses were each adjusted for age, gender and study center. Additionally, cultural background and time point of COVID-19 diagnosis were significantly associated with psychological distress.

In a next step, we evaluated all variables significantly associated in these adjusted analyses as well as several predefined variables within four domain models. The results are presented in Table 2B.

Table 2. Factors associated with psychological distress in patients.

a.

		No psychological distress	Psychological distress	Univariate OR (95%CI)	*p*	Age, gender, center adjusted OR (95%CI)	*p*
		n = 102	n = 24				
Sociodemographic factors							
Age (years)		58.62 (16.10)	56.63 (17.65)	0.99 (0.97, 1.02)	0.590		
Gender	male	68 (66.7%)	8 (33.3%)	1 (Ref)		1 (Ref)	
	female	34 (33.3%)	16 (66.7%)	4 (1.56, 10.27)	**0.004**		
Citizenship	Swiss	71 (69.6%)	15 (62.5%)	1 (Ref)		1 (Ref)	
	Non-Swiss	31 (30.4%)	9 (37.5%)	1.37 (0.54, 3.48)	0.502	1.47 (0.52, 4.11)	0.464
Cultural background	Central/Western Europe	84 (82.4%)	16 (66.7%)	1 (Ref)		1 (Ref)	
	Other	18 (17.6%)	8 (33.3%)	2.33 (0.87, 6.28)	0.093	3.55 (1.03, 12.27)	**0.045**
Religious affiliation	Christian	61 (59.8%)	13 (56.5%)	1 (Ref)		1 (Ref)	
	Non-Christian religion	9 (8.8%)	7 (30.4%)	3.65 (1.15, 11.58)	**0.028**	5.51 (1.38, 22.06)	**0.016**
	No religious affiliation	32 (31.4%)	3 (13.0%)	0.44 (0.12, 1.66)	0.225	0.36 (0.09, 1.43)	0.146
Civil status	Married/ Partnership	66 (64.7%)	14 (58.3%)	1 (Ref)		1 (Ref)	
	Widowed/ separated/single	36 (35.3%)	10 (41.7%)	1.31 (0.53, 3.24)	0.560	0.68 (0.23, 1.94)	0.468
Children	no	30 (30%)	6 (26%)	1 (Ref)		1 (Ref)	
	yes	69 (70%)	17 (74%)	1.23 (0.44, 3.43)	0.690	1.54 (0.51, 4.68)	0.449
Current job situation	Employed	40 (39.6%)	13 (54.2%)	1 (Ref)		1 (Ref)	
	Not employed	43 (45%)	12 (50%)	1.8 (0.74, 4.42)	0.198	2.9 (0.86, 9.74)	0.085
Illness-related factors							
Time point of COVID-19 diagnosis[a], mean (SD)		29.98 (12.39)	33.38 (7.56)	1.03 (0.99, 1.06)	0.202	1.06 (1.01, 1.11)	**0.016**
Duration of hospitalization (days), mean (SD)		9.45 (6.86)	7.08 (4.16)	0.93 (0.84, 1.02)	0.117	0.94 (0.86, 1.04)	0.247
Severity of illness (NEWS score), mean (SD)		6.25 (3.71)	6.04 (3.77)	0.99 (0.87, 1.11)	0.813	1.08 (0.92, 1.26)	0.367
Comorbidity (CCI), mean (SD)		2.44 (2.18)	2.25 (2.17)	0.96 (0.78, 1.18)	0.697	1.01 (0.69, 1.47)	0.964
Self-perceived overall health status (Euroqol), mean (SD)		75.98 (16.30)	65.25 (19.91)	0.97 (0.94, 0.99)	**0.009**	0.97 (0.94, 1)	**0.023**
Antibiotics during hospitalization	no	70 (69.3%)	16 (66.7%)	1 (Ref)		1 (Ref)	
	yes	31 (30.7%)	8 (33.3%)	1.13 (0.44, 2.91)	0.802	1.41 (0.51, 3.92)	0.510
Investigational therapy	no	32 (31.7%)	8 (33.3%)	1 (Ref)		1 (Ref)	
	yes	69 (68.3%)	16 (66.7%)	0.93 (0.36, 2.39)	0.876	1.14 (0.38, 3.38)	0.812
Anxiolytics during hospitalization	no	86 (85.1%)	17 (73.9%)	1 (Ref)		1 (Ref)	
	yes	15 (14.9%)	6 (26.1%)	2.02 (0.69, 5.96)	0.201	2.06 (0.65, 6.52)	0.220
ICU stay	no	85 (83.3%)	22 (91.7%)	1 (Ref)		1 (Ref)	
	yes	17 (16.7%)	2 (8.3%)	0.45 (0.1, 2.12)	0.315	0.61 (0.12, 3.01)	0.542
Intubation	no	91 (89.2%)	23 (95.8%)	1 (Ref)		1 (Ref)	
	yes	11 (10.8%)	1 (4.2%)	0.36 (0.04, 2.93)	0.339	0.49 (0.06, 4.3)	0.518
Psychosocial factors							
Pre-existing psychological comorbidities	no	90 (92%)	14 (58%)	1 (Ref)		1 (Ref)	
	yes	8 (8%)	10 (42%)	8.04 (2.71, 23.83)	**<0.001**	5.73 (1.77, 18.59)	**0.004**
Psychotropic drugs	no	90 (92%)	19 (79%)	1 (Ref)		1 (Ref)	
	yes	8 (8%)	5 (21%)	2.96 (0.87, 10.05)	0.082	2.51 (0.67, 9.4)	0.171

(*Continued*)

Table 2. (Continued)

Resilience (CD-RISC), mean (SD)		32.79 (4.69)	24.53 (7.94)	0.79 (0.71, 0.89)	**<0.001**	0.8 (0.71, 0.91)	**<0.001**
Perceived Stress (PSS), mean (SD)		20.95 (6.43)	29.64 (9.64)	1.17 (1.06, 1.3)	**0.002**	1.18 (1.06, 1.32)	**0.003**
Self-perceived stigmatization (VAS 0–10), mean (SD)		2.49 (3.10)	3.15 (3.53)	1.06 (0.92, 1.24)	0.408	1.05 (0.9, 1.23)	0.507
Consumption of COVID-19 media reports	no	15 (15%)	6 (25%)	1 (Ref)		1 (Ref)	
	yes	82 (85%)	18 (75%)	0.55 (0.19, 1.61)	0.274	0.71 (0.22, 2.28)	0.561
Duration of COVID-19 media consumption, mean (SD)		34.76 (30.51)	40.79 (30.24)	1.01 (0.99, 1.02)	0.436	1.01 (0.99, 1.03)	0.239
Worries due to COVID-19 media reports, mean (SD)		3.56 (2.84)	6.00 (3.79)	1.28 (1.09, 1.5)	**0.002**	1.23 (1.05, 1.45)	**0.012**
Frequency of contacts with relatives	Daily	88 (89%)	16 (67%)	1 (Ref)			
	Less than daily	11 (11%)	8 (33%)	4 (1.39, 11.49)	**0.010**	5.13 (1.6, 16.47)	**0.006**
Type of communication between patients and relatives	Telephone, text and other	58 (59%)	14 (58%)	1 (Ref)			
	Video calls and visits	41 (41%)	10 (42%)	1.01 (0.41, 2.5)	0.982	0.91 (0.29, 2.81)	0.869
Current worries and burdens (VAS 0–10)							
Worried about uncertain prognosis, mean (SD)		5.23 (3.16)	7.04 (3.11)	1.22 (1.04, 1.45)	**0.017**	1.22 (1.03, 1.45)	**0.022**
Burden of isolation measures, mean (SD)		4.67 (3.63)	6.63 (3.32)	1.17 (1.02, 1.34)	**0.022**	1.15 (0.99, 1.33)	0.074
Burden of boredom, mean (SD)		2.96 (3.41)	3.52 (3.36)	1.05 (0.92, 1.2)	0.474	1.03 (0.9, 1.18)	0.683
Worried about health of relatives, mean (SD)		4.36 (3.59)	7.30 (3.10)	1.3 (1.11, 1.52)	**0.001**	1.32 (1.1, 1.57)	**0.002**
Burden of missing relatives, mean (SD)		5.15 (3.61)	6.00 (3.94)	1.07 (0.94, 1.22)	0.326	1.03 (0.89, 1.19)	0.695
Worried about job situation, mean (SD)		1.29 (2.66)	1.91 (3.74)	1.07 (0.93, 1.24)	0.360	1.03 (0.88, 1.22)	0.694
Worried about finances, mean (SD)		0.88 (2.22)	1.78 (3.34)	1.13 (0.96, 1.33)	0.129	1.1 (0.93, 1.31)	0.255
Worried about medical care, mean (SD)		0.55 (1.52)	0.57 (1.50)	1.01 (0.74, 1.36)	0.973	0.95 (0.69, 1.31)	0.761
Other worries, mean (SD)		1.71 (3.42)	1.70 (3.57)	1 (0.87, 1.15)	0.993	1.01 (0.87, 1.18)	0.894
Helpfulness of coping strategies (VAS 0–10)							
Social contacts, mean (SD)		7.79 (2.65)	6.82 (2.99)	0.89 (0.76, 1.04)	0.139	0.85 (0.72, 1.02)	0.074
Distraction, mean (SD)		5.72 (3.52)	4.38 (3.59)	0.9 (0.77, 1.05)	0.174	0.89 (0.76, 1.04)	0.148
Tranquilizers, mean (SD)		0.46 (1.90)	1.36 (3.23)	1.16 (0.91, 1.48)	0.242	1.15 (0.88, 1.51)	0.301
Other, mean (SD)		5.45 (4.31)	6.23 (4.40)	1.04 (0.9, 1.21)	0.552	1.04 (0.89, 1.21)	0.634
Hospital-related factors (VAS 0–10)							
Involvement of psychosocial care team	no	90 (90%	18 (75%)	1 (Ref)		1 (Ref)	
	yes	10 (10.0%)	6 (25.0%)	3 (0.97, 9.3)	0.057	3.1 (0.88, 10.89)	0.078
Contradictory information given by medical team, mean (SD)		0.94 (2.02)	1.17 (1.85)	1.06 (0.85, 1.31)	0.620	0.97 (0.76, 1.23)	0.794
Perceived competence of treating physician, mean (SD)		8.77 (1.41)	8.48 (2.41)	0.91 (0.7, 1.17)	0.460	0.94 (0.71, 1.25)	0.666
Burden of having no visitors, mean (SD)		3.46 (3.34)	5.08 (3.88)	1.14 (1, 1.3)	**0.044**	1.1 (0.96, 1.26)	0.162
Missing physical closeness, mean (SD)		4.33 (3.73)	5.96 (3.77)	1.13 (0.99, 1.27)	0.062	1.1 (0.96, 1.25)	0.160

b.

(*Continued*)

Table 2. (Continued)

		Multivariate model within domains		Overall multivariate model			
		OR (95%CI)	***p***	**OR (95%CI)**	***p***		
Sociodemographic factors							
Age (years)		0.98 (0.95, 1.02)	0.332				
Gender	male	1 (Ref)		1 (Ref)			
	female	5.6 (1.9, 16.5)	**0.002**	1.7 (0.38, 7.71)	0.49		
Cultural background	Central/Western Europe	1 (Ref)					
	Other	1.08 (0.21, 5.54)	0.926				
Religious affiliation	Christian	1 (Ref)		1 (Ref)			
	Non-Christian religion	6.06 (1.1, 33.29)	**0.038**	3.6 (0.38, 33.67)	0.262		
	No religious affiliation	0.35 (0.08, 1.44)	0.144	1.24 (0.19, 7.94)	0.82		
Current job situation	Employed	1 (Ref)		1 (Ref)			
	Not employed	3.84 (1.03, 14.25)	**0.044**	2.99 (0.63, 14.16)	0.169		
Illness-related factors							
Time point of COVID-19 diagnosis[a], mean (SD)		1.03 (0.98, 1.07)	0.246				
Duration of hospitalization (days), mean (SD)		0.9 (0.8, 1.01)	0.084				
Self-perceived overall health status (Euroqol), mean (SD)		0.96 (0.94, 0.99)	**0.008**	0.98 (0.94, 1.02)	0.383		
Anxiolytics during hospitalization	no	1 (Ref)					
	yes	2.71 (0.79, 9.31)	0.112				
ICU stay	no	1 (Ref)					
	yes	1 (0.16, 6.12)	0.996				
Psychosocial factors							
Pre-existing psychological comorbidities	no	1 (Ref)					
	yes	5.41 (0.85, 34.35)	0.073				
Resilience (CD-RISC), mean (SD)		0.83 (0.71, 0.97)	**0.017**	0.82 (0.71, 0.94)	**0.005**		
Perceived Stress (PSS), mean (SD)		1.23 (1.06, 1.42)	0.006	1.21 (1.06, 1.38)	**0.006**		
Worries due to COVID-19 media reports, mean (SD)		1.31 (0.99, 1.72)	0.057				
Frequency of contacts with relatives	Daily	1 (Ref)		1 (Ref)			
	Less than daily	9.57 (1.8, 50.91)	**0.008**	7.67 (1.42, 41.58)	**0.018**		
Current worries and burdens (VAS 0–10)							
Burden of isolation measures, mean (SD)		0.95 (0.72, 1.24)	0.680				
Worried about health of relatives, mean (SD)		1.12 (0.9, 1.4)	0.312				
Helpfulness of coping strategies (VAS 0–10)							
Social contacts, mean (SD)		0.74 (0.56, 0.99)	**0.04**	0.76 (0.57, 1.01)	0.056		
Hospital-related factors (VAS 0–10)							
Involvement of psychosocial care team	no	1 (Ref)					

(*Continued*)

Table 2. (Continued)

	yes	2.59 (0.8, 8.31)	0.111				
Burden of having no visitors, mean (SD)		1.06 (0.86, 1.3)	0.575				
Missing physical closeness, mean (SD)		1.07 (0.88, 1.3)	0.52				

Data are presented as n (%) or mean (standard deviation)

[a]consecutive days, starting with day 0 for first patients hospitalized

Abbreviations: SD, standard deviation; OR, odds ratio; 95%CI, 95% Confidence Interval; COVID-19, Coronavirus disease 2019; CD-RISC, Connor-Davidson Resilience Scale; PSS, Perceived Stress Scale; VAS, visual analogue scale

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The sociodemographic domain model with an area under the receiver-operating characteristic curve (AUC) of 0.77, included the variables age, gender, cultural background, religious affiliation, and current job situation. Of these, being female, non-Christian religion and no employment were independently associated with increased likelihood of psychological distress. In the illness-related factors model containing timepoint of COVID-19 diagnosis, duration of hospitalization, self-perceived overall health status, anxiolytics during hospitalization, and ICU stay (AUC of 0.72), only lower self-perceived overall health status was independently associated. Of the variables pre-existing psychological comorbidities, resilience, perceived stress, worries due to COVID-19 media reports, frequency of contacts with relatives, burden of isolation measures, worries about health of relatives, and social contacts as a coping strategy in the psychosocial domain model (AUC of 0.95), lower resilience, higher perceived stress, lower frequency of contacts with relatives, and lower perceived helpfulness of social contacts as a coping strategy, were each independently associated with higher likelihood of psychological distress. None of the variables, involvement of psychosocial care team, burden of having no visitors and missing physical closeness were independently associated in the fourth domain model (AUC of 0.67).

After including all factors independently associated within these four domain models in a final overall model, only resilience, perceived stress and less than daily frequency of contact with relatives remained independently associated with psychological distress. A model including these three independently associated variables showed very good discrimination regarding presence or absence of psychological distress in patients hospitalized with COVID-19, with an AUC of 0.92.

Psychological distress in relatives 30 days after discharge

In the relative sample, 35 participants (22.9%) met the criteria for psychological distress, i.e., showed symptoms of depression and/or anxiety defined by a score of $\geq$8 on the depression and/or anxiety subscale of the HADS. Of those, 25 had symptoms of anxiety (16.3%) and 23 had symptoms of depression (15%).

Table 3A and 3B provide an overview of the different variables and associations with psychological distress.

In univariate models (Table 3A), we found several factors associated with psychological distress, including sociodemographic factors, i.e., having children, not being employed, illness-related factors, i.e., lower self-perceived overall health status, death of patient, psychosocial factors, i.e., use of psychotropic drugs, lower resilience, higher perceived stress, communicating through video calls or being able to visit the patient, higher perceived overall burden, increased worries about uncertain diagnosis and infection, higher burden of isolation measures and

Table 3. Factors associated with psychological distress in relatives.

a.

		No Psychological distress	Psychological distress	Univariate model, OR (95%CI)	*p*	Age, gender, center adjusted model, OR (95%CI)	*p*
		n = 118	n = 35				
Sociodemographic factors							
Age (years)		56.98 (14.91)	60.09 (15.01)	1.01 (0.99, 1.04)	0.281		
Gender	male	31 (26.3%)	7 (20.0%)	1 (Ref)			
	female	87 (73.7%)	28 (80.0%)	1.43 (0.57, 3.59)	0.452		
Citizenship	Swiss	96 (81.4%)	29 (82.9%)	1 (Ref)		1 (Ref)	
	Non-Swiss	22 (18.6%)	6 (17.1%)	0.9 (0.33, 2.44)	0.840	0.98 (0.35, 2.75)	0.966
Cultural background	Central/Western Europe	93 (78.8%)	28 (80.0%)	1 (Ref)		1 (Ref)	
	Other	25 (21.2%)	7 (20.0%)	0.93 (0.36, 2.38)	0.880	1.11 (0.39, 3.18)	0.842
Religious affiliation	Christian	79 (67.5%)	25 (71.4%)	1 (Ref)		1 (Ref)	
	Non-Christian religion	10 (8.5%)	3 (8.6%)	0.95 (0.24, 3.72)	0.939	1.03 (0.24, 4.42)	0.963
	No religious affiliation	28 (23.9%)	7 (20.0%)	0.79 (0.31, 2.03)	0.624	0.83 (0.31, 2.19)	0.705
Civil status	Married/ Partnership	87 (74.4%)	23 (65.7%)	1 (Ref)		1 (Ref)	
	Widowed/ separated/single	30 (25.6%)	12 (34.3%)	1.51 (0.67, 3.41)	0.318	1.5 (0.66, 3.41)	0.332
Children	no	35 (29.7%)	4 (11.4%)	1 (Ref)		1 (Ref)	
	yes	83 (70.3%)	31 (88.6%)	3.27 (1.07, 9.95)	**0.037**	3.16 (1.02, 9.81)	**0.046**
Current job situation	Employed	69 (58.5%)	12 (35.3%)	1 (Ref)		1 (Ref)	
	Not employed	49 (41.5%)	22 (64.7%)	2.58 (1.17, 5.71)	**0.019**	2.97 (1.07, 8.3)	**0.037**
Illness-related factors							
Relative quarantined	no	55 (56%)	13 (39%)	1 (Ref)		1 (Ref)	
	yes	44 (44%)	20 (61%)	1.92 (0.86, 4.29)	0.110	1.94 (0.86, 4.37)	0.110
Relative ill with COVID-19	no	73 (63.5%)	24 (72.7%)	1 (Ref)		1 (Ref)	
	yes	42 (36.5%)	9 (27.3%)	0.65 (0.28, 1.53)	0.326	0.72 (0.3, 1.71)	0.455
Self-perceived overall health status (Euroqol), mean (SD)		84.89 (13.28)	70.41 (20.73)	0.95 (0.93, 0.97)	<**0.001**	0.95 (0.93, 0.97)	<**0.001**
Time point of COVID-19 diagnosis[a], mean (SD)		30.04 (12.06)	30.26 (13.99)	1 (0.97, 1.03)	0.929	1 (0.97, 1.04)	0.774
Death of patient	no	103 (87.3%)	24 (68.6%)	1 (Ref)		1 (Ref)	
	yes	15 (12.7%)	11 (31.4%)	3.15 (1.28, 7.71)	**0.012**	3.8 (1.37, 10.55)	**0.010**
Psychosocial factors							
Relationship with patient	Patient is partner	60 (50.8%)	17 (48.6%)	1 (Ref)		1 (Ref)	
	Patient is child	6 (5.1%)	6 (17.1%)	3.53 (1.01, 12.36)	**0.049**	3.16 (0.88, 11.39)	0.079
	Patient is parent	28 (23.7%)	9 (25.7%)	1.13 (0.45, 2.86)	0.789	1.55 (0.54, 4.47)	0.417
	Other	24 (20.3%)	3 (8.6%)	0.44 (0.12, 1.64)	0.223	0.42 (0.11, 1.59)	0.203
Relative living in same household with patient	no	54 (45.8%)	16 (45.7%)	1 (Ref)		1 (Ref)	
	yes	64 (54.2%)	19 (54.3%)	1 (0.47, 2.14)	0.996	0.97 (0.45, 2.08)	0.929
Frequency of contact with patient	Daily	74 (63.2%)	23 (65.7%)	1 (Ref)		1 (Ref)	
	Less than daily	43 (36.8%)	12 (34.3%)	0.9 (0.41, 1.98)	0.790	0.95 (0.42, 2.11)	0.892
Relative sought out psychological help	no	109 (95.6%)	33 (94.3%)	1 (Ref)		1 (Ref)	
	yes	5 (4.4%)	2 (5.7%)	1.32 (0.24, 7.13)	0.746	1.29 (0.23, 7.11)	0.774

(*Continued*)

Table 3. (Continued)

Pre-existing psychological comorbidities	no	101 (88.6%)	30 (85.7%)	1 (Ref)		1 (Ref)	
	yes	13 (11.4%)	5 (14.3%)	1.29 (0.43, 3.93)	0.648	1.18 (0.38, 3.66)	0.772
Psychotropic drugs	no	104 (92.0%)	26 (74.3%)	1 (Ref)		1 (Ref)	
	yes	9 (8.0%)	9 (25.7%)	4 (1.44, 11.08)	**0.008**	3.83 (1.35, 10.9)	**0.012**
Resilience (CD-RISC), mean (SD)		31.93 (4.32)	27.56 (7.18)	0.86 (0.79, 0.94)	**<0.001**	0.86 (0.78, 0.94)	**0.001**
Perceived Stress (PSS), mean (SD)		21.95 (5.87)	28.30 (9.07)	1.14 (1.06, 1.23)	**<0.001**	1.18 (1.08, 1.28)	**<0.001**
Type of communication between relatives and patients	Telephone, text and other	77 (69.4%)	13 (40.6%)	1 (Ref)		1 (Ref)	
	Video calls & visits	34 (30.6%)	19 (59.4%)	3.31 (1.47, 7.46)	**0.004**	3.68 (1.58, 8.58)	**0.002**
Consumption of COVID-19 media reports	no	6 (8%)	2 (8%)	1 (Ref)		1 (Ref)	
	yes	74 (93%)	22 (92%)	0.89 (0.17, 4.74)	0.893	0.7 (0.12, 4.09)	0.696
Duration of COVID-19 media consumption, mean (SD)		54.44 (48.96)	60.24 (67.02)	1 (0.99, 1.01)	0.669	1 (0.99, 1.01)	0.868
Worries due to COVID-19 media reports, mean (SD)		5.00 (3.12)	6.22 (3.04)	1.14 (0.97, 1.34)	0.105	1.13 (0.97, 1.33)	0.118
Current worries and burdens (VAS 0–10)							
Perceived overall burden due to COVID-19, mean (SD)		5.16 (2.91)	8.24 (2.05)	1.66 (1.33, 2.06)	**<0.001**	1.76 (1.39, 2.23)	**<0.001**
Worried about uncertain prognosis, mean (SD)		4.87 (3.38)	6.59 (3.91)	1.16 (1.02, 1.32)	**0.024**	1.19 (1.03, 1.37)	**0.015**
Worried about infection, mean (SD)		2.59 (2.83)	4.09 (3.95)	1.15 (1.02, 1.3)	**0.021**	1.18 (1.04, 1.34)	**0.013**
Burden of isolation measures, mean (SD)		3.94 (3.12)	7.19 (3.31)	1.38 (1.19, 1.6)	**<0.001**	1.39 (1.19, 1.62)	**<0.001**
Burden of separation from patient, mean (SD)		5.62 (3.21)	7.29 (3.49)	1.19 (1.03, 1.36)	**0.017**	1.23 (1.06, 1.42)	**0.008**
Other worries, mean (SD)		6.17 (4.27)	7.95 (3.46)	1.13 (0.98, 1.3)	0.096	1.12 (0.97, 1.3)	0.120
Helpfulness of coping strategies (VAS 0–10)							
Social contacts, mean (SD)		7.80 (2.74)	7.94 (2.33)	1.02 (0.88, 1.19)	0.799	1.04 (0.88, 1.24)	0.626
Distraction, mean (SD)		6.37 (3.54)	6.68 (3.11)	1.03 (0.91, 1.16)	0.657	1.03 (0.91, 1.18)	0.609
Tranquilizers, mean (SD)		0.78 (2.25)	1.67 (3.06)	1.13 (0.98, 1.31)	0.094	1.13 (0.97, 1.31)	0.111
Alcohol consumption, mean (SD)		0.66 (1.70)	0.07 (0.37)	0.5 (0.2, 1.24)	0.133	0.5 (0.2, 1.25)	0.137
Relaxation techniques, mean (SD)		2.62 (3.78)	2.58 (3.69)	1 (0.9, 1.11)	0.961	1.01 (0.89, 1.13)	0.933
Sports, mean (SD)		5.23 (4.16)	2.43 (3.65)	0.84 (0.75, 0.94)	**0.002**	0.82 (0.72, 0.93)	**0.002**
Other, mean (SD)		7.94 (3.64)	6.60 (4.10)	0.92 (0.81, 1.04)	0.166	0.91 (0.8, 1.03)	0.130
Hospital-related factors							
Involvement of psychosocial care team	no	108 (95.6%)	30 (85.7%)	1 (Ref)		1 (Ref)	
	yes	5 (4.4%)	5 (14.3%)	3.6 (0.98, 13.26)	0.054	3.22 (0.83, 12.5)	0.091
Relative was in contact with medical team	no	49 (43.8%)	8 (22.9%)	1 (Ref)		1 (Ref)	
	yes	63 (56.3%)	27 (77.1%)	2.62 (1.1, 6.28)	**0.030**	2.86 (1.18, 6.93)	**0.020**
Satisfaction with communication with medical team, mean (SD)		7.98 (2.83)	8.36 (2.58)	1.05 (0.88, 1.26)	0.562	1.01 (0.83, 1.23)	0.915
Relative received information regarding prognosis	no	34 (53%)	7 (27%)	1 (Ref)		1 (Ref)	
	yes	30 (47%)	19 (73%)	3.08 (1.14, 8.33)	**0.027**	3.79 (1.33, 10.79)	**0.012**
Medical care was perceived as	Sufficient	52 (81%)	19 (76%)	1 (Ref)		1 (Ref)	
	Inadequate	12 (19%)	6 (24%)	1.37 (0.45, 4.16)	0.580	1.55 (0.48, 5.05)	0.468
Comprehensibility of medical information, mean (SD)		8.22 (2.99)	8.54 (2.50)	1.04 (0.88, 1.24)	0.636	0.99 (0.81, 1.21)	0.909

(*Continued*)

Table 3. (Continued)

Relative received recommendations regarding own care	no	43 (67%)	17 (68%)	1 (Ref)		1 (Ref)	
	yes	21 (33%)	8 (32%)	0.96 (0.36, 2.59)	0.941	1.15 (0.41, 3.24)	0.785
Burden of not being able to visit patient (VAS 0–10), mean (SD)		5.78 (3.45)	7.65 (3.17)	1.2 (1.04, 1.37)	**0.010**	1.19 (1.03, 1.36)	**0.014**
Missing physical closeness (VAS 0–10), mean (SD)		4.92 (3.82)	7.06 (3.79)	1.17 (1.04, 1.31)	**0.009**	1.16 (1.03, 1.31)	**0.015**

b.

		Multivariate model within domains		**Overall multivariate model**	
		OR (95% CI)	***p***	**OR (95% CI)**	***p***
Sociodemographic factors					
Children	no	1 (Ref)		1 (Ref)	
	yes	3.37 (1.09, 10.4)	**0.035**	2.91 (0.72, 11.73)	0.132
Current job situation	Employed	1 (Ref)		1 (Ref)	
	Not employed	2.45 (1.11, 5.39)	**0.027**	1.47 (0.51, 4.21)	0.473
Illness-related factors					
Relative quarantined	no	1 (Ref)			
	yes	1.98 (0.85, 4.61)	0.111		
Self-perceived overall health status (Euroqol), mean (SD)		0.95 (0.93, 0.98)	<**0.001**	0.97 (0.94, 1.01)	0.131
Death of patient	no	1 (Ref)		1 (Ref)	
	yes	2.84 (1.06, 7.63)	**0.038**	1.14 (0.29, 4.45)	0.846
Psychosocial factors					
Relationship with patient	Patient is partner	1 (Ref)			
	Patient is child	1.92 (0.18, 20.87)	0.593		
	Patient is parent	1.89 (0.52, 6.92)	0.334		
	Other	0.33 (0.05, 2.01)	0.230		
Psychotropic drugs	no	1 (Ref)			
	yes	1.1 (0.21, 5.75)	0.913		
Resilience (CD-RISC), mean (SD)		0.81 (0.7, 0.94)	**0.005**	0.85 (0.75, 0.96)	**0.007**
Perceived Stress (PSS), mean (SD)		0.9 (0.79, 1.04)	0.145		
Type of communication between relatives and patients	Telephone, text and other	1 (Ref)			
	Video calls & visits	2.91 (0.89, 9.51)	0.078		
Current worries and burdens (VAS 0–10)					
Perceived overall burden due to COVID-19, mean (SD)		1.84 (1.36, 2.48)	<**0.001**	1.72 (1.31, 2.25)	<**0.001**
Worried about uncertain prognosis, mean (SD)		1 (0.81, 1.22)	0.964		
Worried about infection, mean (SD)		1.19 (0.98, 1.46)	0.079		
Burden of isolation measures, mean (SD)		1.22 (0.97, 1.53)	0.087		
Burden of separation from patient, mean (SD)		0.89 (0.69, 1.16)	0.386		
Helpfulness of coping strategies (VAS 0–10)					
Sports, mean (SD)		0.81 (0.68, 0.97)	**0.018**	0.89 (0.78, 1.02)	0.100
Hospital-related factors					

(*Continued*)

Table 3. (Continued)

Relative was in contact with medical team	no	1 (Ref)			
	yes	2.46 (0.97, 6.22)	0.057		
Relative received information regarding prognosis	no	1 (Ref)			
	yes	2.3 (0.99, 5.34)	0.053		
Burden of not being able to visit patient (VAS 0–10), mean (SD)		1.17 (0.99, 1.39)	0.068		
Missing physical closeness (VAS 0–10), mean (SD)		1.1 (0.95, 1.27)	0.208		

Data presented as n (%) or mean (standard deviation)

[a]consecutive days, starting with day 0 for first patients hospitalized

Abbreviations: SD, standard deviation; OR, Odds Ratio; 95% CI, 95% Confidence Interval; COVID-19, Coronavirus disease 2019; CD-RISC, Connor-Davidson Resilience Scale; PSS, Perceived Stress Scale

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separation from patient, sport as coping strategy, and hospital-related factors, i.e., relative was in contact with medical team, received information regarding prognosis, higher burden of not being able to visit patient, and missing physical closeness. Each of these factors remained significantly associated with psychosocial distress when adjusted for age, gender and study center.

In the multivariate analyses, several independently related factors emerged as illustrated in Table 3B. In the sociodemographic domain model, each of the two included variables, i.e., having children and not being employed, was associated with psychological distress. The AUC of this model was 0.66. In the illness-related factors model including self-perceived stress, if the relative was in quarantine and if the patient had died (AUC of 0.77), lower perceived overall health status and death of the patient were independently associated. In the psychosocial model, i.e., relationship with patient, psychotropic drugs, resilience, perceived stress, type of communication, perceived overall burden, worries about uncertain prognosis and infection, burden of isolation measures and separation from patient as well as sport as coping strategy, with an AUC of 0.92, higher resilience, higher perceived overall burden and helpfulness of sport as coping strategy were associated with psychological distress above and beyond the effects of the other factors in the model. The hospital-related factors model included the variables contact with medical team, receiving information regarding prognosis, burden of not being able to visit the patient and missing physical closeness (AUC 0.77). None of these were independently associated with the outcome.

In the final overall model containing all variables independently associated within the latter four domain models, only higher resilience and higher perceived overall burden caused by COVID-19 remained significantly, independently associated with the psychological distress. The model showed very good discrimination regarding relatives with and without psychological distress, with an AUC of 0.87.

PTSD in patients and relatives 30 days after discharge

In total, 115 patients completed the IES-r questionnaire and could be included in the analyses. Ten patients (8.7%) showed considerable symptoms of PTSD. In univariate analyses, several factors in the domains of sociodemographic, psychosocial and hospital-related factors were associated with presence of clinically relevant symptoms of PTSD. In the sociodemographic domain these were lower age, female gender, non-swiss citizenship, non-central/western European cultural background, and non-Christian religion. In the psychosocial domain, lower

resilience, higher perceived stress, increased worries due to COVID-19 media reports and about uncertain prognosis, as well as higher burden of isolation measures and of missing relatives each were associated with clinically relevant symptoms of PTSD. The hospital-related factors contradictory information given by medical team and higher burden of having no visitors were also associated. When age, gender and study center were added as covariates to each of these univariate analyses, only non-Swiss citizenship, non-central/western European background and higher worries due to COVID-19 media reports remained significant. A multivariate model containing these factors showed good discrimination, with an AUC of 0.84 (Table 4). The factor worries due to COVID-19 media reports was independently associated with clinically relevant symptoms of PTSD.

Only three relatives (2%) showed clinically relevant symptoms of PTSD. Due to the low number of events, no regression models were calculated.

Discussion

In this Swiss prospective observational cohort study assessing the prevalence of psychological distress and potentially associated factors among COVID-19 patients and their relatives after hospital discharge, we found considerable rates of psychological distress in both groups which are higher than those among the Swiss general population in 2017 [77] as well as those of a large sample of the Swiss general population during the COVID-19 pandemic [21, 22]. Importantly, several associated factors were identified and some of these psychosocial and isolation-related factors seem to be addressable during routine hospital care and might be at least partially modifiable. Several points of our analysis deserve further comment.

First, the prevalence of psychological distress in our patient sample is in line with the results from Wu et al. [78] and Zhang et al. [79], who were among the first to evaluate psychological outcome in Chinese COVID-19 patients. Wu et al found 14% and 11% of patients to show at least mild symptoms [78], whereas Zhang et al found 21% and 29% [79] to show at least moderate symptoms of anxiety and depression, respectively. Bo et al. [33] found in an observational study which included 714 patients in China that almost all (96.2%) reported symptoms of PTSD during hospitalization. It must be noted that these symptoms do not reflect a PTSD diagnosis and findings may therefore not be interpreted as the rate of PTSD in this sample. The lower rate of patients with high PTSD symptom levels in our sample may be explained by the later time point at which patients were assessed. The higher rate reported by Bo et al. [33] may thus reflect symptoms of acute stress due to COVID-19 and isolation remitting within one month [80]. This is in line with symptoms of acute stress disorder remitting within one month after a traumatic event, and only a minority of patients developing full PTSD [80]. Our study reveals that relatives of COVID-19 patients might be affected to a similar extent, with 22.9% showing psychological distress and 16.3% and 15% showing symptoms of anxiety and depression, respectively. Studies evaluating the general population during the current pandemic found considerably high and increased levels of psychological distress [18, 19, 21–23, 25, 30, 31, 81–83], potentially related to environmental factors such as quarantine [12, 84], socioeconomic effects, and the risk of infection. However, several longitudinal studies did not find an increase in psychological distress in the general population before and during the first months of the pandemic [27–29]. First studies further differentiating between individuals who have a relative with COVID-19 and those who do not, suggest that having a sick relative causes significantly higher levels of distress [46.7 vs. 27.7%; 79, 84, 85]. These individuals might therefore require increased clinical attention tailored to their needs in order to prevent adverse long-term psychological burden [85–87].

Table 4. Factors associated with high PTSD symptom levels in patients.

a.

		No/few PTSD symptoms	High PTSD symptom levels	Univariate model OR (95%CI)	*p*	Age, gender, center adjusted model, OR (95% CI)	*p*
		n = 105	n = 10				
Sociodemographic factors							
Age (years)		58.28 (15.66)	44.40 (14.14)	0.95 (0.91, 0.99)	**0.013**		
Gender	male	71 (67.6%)	1 (10%)	1 (Ref)			
	female	34 (32.7%)	9 (90.0%)	18.53 (2.25, 152.26)	**0.007**		
Citizenship	Swiss	74 (71.2%)	3 (30.0%)	1 (Ref)		1 (Ref)	
	Non-Swiss	30 (28.8%)	7 (70.0%)	5.76 (1.39, 23.75)	**0.016**	9.83 (1.62, 59.64)	**0.013**
Cultural background	Central/Western Europe	86 (82.7%)	5 (50.0%)	1 (Ref)		1 (Ref)	
	Other	18 (17.3%)	5 (50.0%)	4.78 (1.25, 18.24)	**0.022**	15.05 (1.3, 174.21)	**0.030**
Religious affiliation	Christian	61 (58.7%)	5 (50.0%)	1 (Ref)		1 (Ref)	
	Non-Christian religion	10 (9.6%)	4 (40.0%)	4.88 (1.12, 21.33)	**0.035**	8.62 (0.75, 99.52)	0.084
	No religious affiliation	33 (31.7%)	1 (10.0%)	0.37 (0.04, 3.3)	0.373	0.24 (0.02, 2.68)	0.249
Civil status	Married/ Partnership	69 (66.3%)	5 (50.0%)	1 (Ref)		1 (Ref)	
	Widowed/ separated/single	35 (33.7%)	5 (50.0%)	1.97 (0.53, 7.27)	0.308	0.67 (0.14, 3.31)	0.621
Children	no	30 (29.7%)	3 (30%)	1 (Ref)		1 (Ref)	
	yes	71 (70.3%)	7 (70.0%)	1 (0.24, 4.13)	1.000	3.36 (0.47, 24)	0.226
Current job situation	Employed	53 (54%)	8 (80%)	1 (Ref)		1 (Ref)	
	Not employed	46 (46%)	2 (20%)	0.29 (0.06, 1.43)	0.127	0.56 (0.08, 4.04)	0.567
Illness-related factors							
Timepoint of COVID-19 diagnosis[a], mean (SD)		31.27 (12.02)	26.50 (11.49)	0.97 (0.91, 1.02)	0.229	1.03 (0.95, 1.12)	0.497
Duration of hospitalization (days), mean (SD)		9.14 (6.51)	6.40 (3.98)	0.89 (0.75, 1.06)	0.204	0.9 (0.73, 1.12)	0.337
Severity of illness (NEWS score), mean (SD)		6.31 (3.76)	5.20 (3.26)	0.92 (0.77, 1.1)	0.370	1.1 (0.86, 1.41)	0.454
Comorbidity (CCI), mean (SD)		2.40 (2.17)	0.90 (1.20)	0.61 (0.38, 1)	0.050	0.76 (0.33, 1.76)	0.528
Self-perceived overall health status (Euroqol), mean (SD)		75.2 (16.39)	64.1 (18.95)	0.96 (0.93, 1)	0.053	0.97 (0.93, 1.02)	0.261
Antibiotics during hospitalization	no	70 (67.3%)	8 (80%)	1 (Ref)		1 (Ref)	
	yes	34 (32.7%)	2 (20.0%)	0.51 (0.1, 2.56)	0.417	0.7 (0.11, 4.6)	0.707
Investigational therapy	no	29 (27.9%)	5 (50%)	1 (Ref)		1 (Ref)	
	yes	75 (72.1%)	5 (50.0%)	0.39 (0.1, 1.44)	0.156	0.43 (0.08, 2.35)	0.328
Anxiolytics during hospitalization	no	88 (85.4%)	6 (60%)	1 (Ref)		1 (Ref)	
	yes	15 (14.6%)	4 (40.0%)	3.91 (0.99, 15.52)	0.052	3.18 (0.56, 17.97)	0.190
ICU stay	no	89 (84.8%)	8 (80%)	1 (Ref)		1 (Ref)	
	yes	16 (15.2%)	2 (20.0%)	1.39 (0.27, 7.16)	0.693	2.5 (0.31, 19.82)	0.387
Intubation	no	95 (90.5%)	9 (90%)	1 (Ref)		1 (Ref)	
	yes	10 (9.5%)	1 (10.0%)	1.06 (0.12, 9.21)	0.961	1.14 (0.07, 17.82)	0.926
Psychosocial factors							
Pre-existing psychological comorbidities	no	90 (87.4%)	7 (70%)	1 (Ref)		1 (Ref)	
	yes	13 (12.6%)	3 (30.0%)	2.97 (0.68, 12.93)	0.148	1.11 (0.2, 6.03)	0.906

(*Continued*)

Table 4. (Continued)

Psychotropic drugs	no	94 (90.4%)	8 (80%)	1 (Ref)		1 (Ref)	
	yes	10 (9.6%)	2 (20.0%)	2.35 (0.44, 12.62)	0.319	1.37 (0.18, 10.37)	0.761
Resilience (CD-RISC), mean (SD)		32.08 (5.53)	26.00 (9.26)	0.88 (0.79, 0.97)	**0.010**	0.94 (0.82, 1.07)	0.360
Perceived Stress (PSS), mean (SD)		21.10 (6.73)	34.50 (6.16)	1.3 (1.08, 1.57)	**0.005**	78.64 (0.04, 160746.13)	0.262
Self-perceived stigmatization (VAS 0–10), mean (SD)		2.58 (3.16)	3.50 (3.33)	1.09 (0.85, 1.39)	0.492	1.07 (0.82, 1.4)	0.597
Consumption of COVID-19 media reports	no	17 (16.8%)	2 (20%)	1 (Ref)		1 (Ref)	
	yes	84 (83.2%)	8 (80.0%)	0.81 (0.16, 4.15)	0.800	1.42 (0.21, 9.83)	0.720
Duration of COVID-19 media consumption mean (SD)		36.29 (31.38)	41.88 (29.75)	1.01 (0.98, 1.03)	0.627	1.02 (0.99, 1.05)	0.231
Worries due to COVID-19 media reports, mean (SD)		3.77 (3.06)	7.00 (3.16)	1.4 (1.09, 1.81)	**0.008**	1.36 (1.02, 1.82)	**0.039**
Frequency of contacts with relatives	Daily	88 (86.3%)	9 (90.0%)	1 (Ref)		1 (Ref)	
	Less than daily	14 (13.7%)	1 (10.0%)	0.7 (0.08, 5.95)	0.743	1.13 (0.11, 11.79)	0.916
Type of communication between patients and relatives	Telephone, text and other	59 (57.8%)	6 (60.0%)	1 (Ref)		1 (Ref)	
	Video calls and visits	43 (42.2%)	4 (40.0%)	0.91 (0.24, 3.44)	0.895	0.38 (0.06, 2.52)	0.318
Current worries and burden (VAS 0–10)							
Worries about uncertain prognosis, mean (SD)		5.52 (3.15)	8.30 (1.95)	1.56 (1.08, 2.23)	**0.017**	1.41 (0.95, 2.09)	0.091
Burden of isolation measures, mean (SD)		4.74 (3.61)	7.40 (3.17)	1.27 (1.01, 1.58)	**0.039**	1.11 (0.86, 1.43)	0.439
Burden of boredom, mean (SD)		2.87 (3.29)	4.00 (3.77)	1.1 (0.91, 1.33)	0.333	0.9 (0.68, 1.19)	0.466
Worries about health of relatives, mean (SD)		4.87 (3.59)	6.90 (3.51)	1.19 (0.97, 1.47)	0.102	1.08 (0.84, 1.41)	0.539
Burden of missing relatives, mean (SD)		5.07 (3.67)	7.80 (3.01)	1.3 (1.01, 1.68)	**0.041**	1.14 (0.87, 1.48)	0.345
Worries about job situation, mean (SD)		1.37 (2.81)	1.60 (3.37)	1.03 (0.83, 1.28)	0.807	0.81 (0.6, 1.1)	0.184
Worries about finances, mean (SD)		0.93 (2.34)	1.80 (3.01)	1.13 (0.91, 1.4)	0.285	1.07 (0.82, 1.39)	0.616
Worries about medical care, mean (SD)		0.62 (1.59)	0	n.a.	n.a.	n.a.	n.a.
Other worries, mean (SD)		1.93 (3.60)	0.80 (2.53)	0.88 (0.68, 1.15)	0.350	0.91 (0.68, 1.22)	0.518
Helpfulness of coping strategies (VAS 0–10)							
Social contacts, mean (SD)		7.65 (2.64)	8.11 (1.83)	1.08 (0.8, 1.45)	0.610	1.03 (0.72, 1.47)	0.865
Distraction, mean (SD)		5.59 (3.52)	4.50 (3.67)	0.92 (0.73, 1.16)	0.466	0.84 (0.62, 1.14)	0.271
Tranquilizers, mean (SD)		0.44 (1.86)	3.33 (5.77)	1.31 (0.97, 1.76)	0.073	n.a.	n.a.
Other, mean (SD)		5.97 (4.22)	6.00 (4.00)	1 (0.79, 1.28)	0.989	0.94 (0.67, 1.32)	0.720
Hospital-related factors (VAS 0–10)							
Involvement of psychosocial care team	no	92 (88.5%)	8 (80%)	1 (Ref)		1 (Ref)	
	yes	12 (11.5%)	2 (20.0%)	1.92 (0.36, 10.1)	0.443	0.77 (0.09, 6.49)	0.806
Contradicting information given by medical team, mean (SD)		0.88 (1.85)	2.60 (3.03)	1.33 (1.04, 1.69)	**0.022**	1.06 (0.78, 1.44)	0.715
Perceived competence of treating physician, mean (SD)		8.79 (1.41)	8.50 (1.84)	0.88 (0.57, 1.34)	0.543	1.07 (0.67, 1.72)	0.774
Burden of having no visitors, mean (SD)		3.53 (3.32)	6.70 (3.37)	1.32 (1.07, 1.64)	**0.010**	1.18 (0.93, 1.49)	0.179

(*Continued*)

Table 4. (Continued)

Missing physical closeness (VAS 0–10), mean (SD)		4.61 (3.69)	6.70 (3.62)	1.18 (0.97, 1.44)	0.101	1.07 (0.87, 1.32)	0.514
b.							
		Multivariate overall model					
		OR (95%CI)	***p***				
Sociodemographic factors							
Citizenship	Swiss	1 (Ref)					
	Non-Swiss	4.24 (0.78, 23.08)	0.095				
Cultural background	Central/Western Europe	1 (Ref)					
	Other	1.38 (0.25, 7.50)	0.38				
Psychosocial factors							
Worries due to COVID-19 media reports, mean (SD)		1.40 (1.08, 1.81)	**0.010**				

Data presented as n (%) or mean (standard deviation). Abbreviations: SD, standard deviation; OR, Odds Ratio; 95% CI, 95% Confidence Interval; COVID-19, Coronavirus disease 2019; NEWS, National Early Warning Score; CCI, Charlson Comorbidity Index; ICU, Intensive Care Unit; COVID-19, Coronavirus disease 2019; CD-RISC, Connor-Davidson Resilience Scale; PSS, Perceived Stress Scale; VAS, Visual Analogue Scale.

[a]consecutive days, starting with day 0 for first patients hospitalized

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Second, we identified several factors associated with psychological distress. Regarding gender disparities in the general population, woman are twice as likely to develop psychological sequelae [88]. In line with this and the findings of Wu et al. [89], female patients were more likely than males to report increased levels of psychological distress. Interestingly, this association was present for patients but not for relatives. This is in contrast to previous literature focusing on relatives of critically ill patients, in which being female was considered an important risk factor for psychological burden in relatives [58, 90, 91]. However, these studies focused on relatives of patients hospitalized in the ICU for a variety of reasons not related to COVID-19, and outcomes were measured three months after ICU discharge, which may limit the comparability with our specific population of relatives having a loved one hospitalized for COVID-19 [91]. Research on relatives of ICU patients has also shown that the likelihood of a high psychological burden was up to 18 times higher in relatives who felt that they were given incomplete information regarding their loved one [45, 58] or in relatives whose loved one died in the ICU [58, 92, 93]. This is in line with our finding that relatives of COVID-19 patients had more psychological distress and depression if the patient had died. The effect of patient outcomes on family members' psychological burden is still a controversial topic in the literature, with some studies reporting no association between patient death and relatives' psychological outcome, such as PTSD [45, 94]. However, a recent Dutch study found that people bereaved due to COVID-19 appear to have higher levels of prolonged grief disorder as well as persistent complex bereavement disorder compared to natural bereavement but not unnatural bereavement [95]. COVID-19 may be considered an unnatural and unexpected type of death which could explain the increased levels of distress in bereaved relatives in our study potentially leading to an increase in grief disorders during the COVID-19 pandemic.

Interestingly, while previous research has shown that patients with serious illnesses or hospitalization in the ICU are at increased risk of developing psychological sequelae [49, 96, 97], such associations were not found in our sample. In fact, apart from death of the patient, other illness-related factors such as comorbidity, severity of illness, ICU stay or mechanical

ventilation were not associated with patients' or relatives' psychological outcomes. Psychological distress, however, was associated with subjective overall health in both patients and relatives, emphasizing the significance of considering an individual's self-perception of their current health.

Further, relatives who were not employed were more likely to experience psychological distress than working relatives as expected based on general knowledge of the negative impact of unemployment on mental health across populations. In line with this, Shi et al. [84] identified employment as a potential protective factor in family members suffering from anxiety or depression in a large sample of the Chinese general population during the pandemic.

Among psychosocial factors, access to media coverage of COVID-19 was found to be a potential risk factor in prior studies [98], and concerns have been raised by leading mental health experts [47, 51, 99]. Previous research has shown that viewing media coverage of mass trauma may increase long-term distress [100, 101]. Hence, in persons at risk of distress, reducing media overconsumption might be beneficial.

Also, patients who reported higher perceived stress (i.e., experienced increased levels of perceived helplessness and lower levels of self-efficacy) and relatives who reported higher overall burden due to COVID-19 were more likely to show psychological distress. Patients who had daily contact with relatives or received support from personal social networks and patients with higher levels of resilience appeared to have lower levels of psychological distress.

Interestingly, frequency of contact with relatives showed a strong association with psychological distress and is potentially modifiable. While quarantine measures normally do not allow modifications, regular interaction with relatives might act as a protective factor in the development of psychological distress. Such interactions could also be done using new technology including face-to-face interactions over the smartphone or other devices. Current research into effective interventions to reduce depression and anxiety suggests that physical exercise is a potentially effective coping strategy and could be used during a lockdown [102–105].

Third, for both patients and relatives, resilience emerged as the most relevant factor associated with psychological distress and high PTSD symptom levels according to the DSM. However, both variables were assessed simultaneously and thus no causal conclusions can be made. Resilience may be defined as a person's emotional and mental capacity to adapt well when experiencing critical life events [106–108]. With regard to resilience during the COVID-19 pandemic, leading mental health experts emphasize the need for access to mental health support [109–112] and the World Health Organization recently published specific recommendations [113, 114]. The latter are divided in several sections which are addressed to the general population, health care workers and team leaders, caretakers and people in isolation, respectively. They include short information and psychoeducation elements as well as specific recommendations and coping strategies, adapted to the current pandemic. Future research should evaluate whether interventions targeting core factors of resilience such as coping through social support and facilitating higher perceived self-efficacy are able to reduce the negative psychological impact of COVID-19.

Finally, we are aware of some limitations. As this is an observational study it is only hypotheses generating. Further, due to language barriers, death and restricted accessibility, we could not include all consecutive patients and relatives, potentially inducing a selection bias. Therefore, our data need confirmation in a larger cohort of patients and relatives. Due to the clinical circumstances of COVID-19 and patients' hospitalization such as isolation measures and the sudden and rapidly increasing number of cases in early March 2020, it was neither feasible to assess patients nor all relatives during patients' hospitalization. We thus contacted patients and

relatives at 30 days after discharge and asked for recalled information regarding baseline and follow-up, which could introduce recall bias.

Conclusions

A considerable proportion of COVID-19 patients as well as their relatives show symptoms of psychological distress 30 days after hospital discharge. Several psychosocial and isolation-related factors such as resilience, perceived stress, frequency of contact with relatives and worries due to media reports were associated with adverse outcome and are at least partially modifiable. Along with previously known risk factors for psychological distress in hospitalized patients, our findings could be used to identify patients and relatives at increased risk of experiencing psychological distress over the long term, and to tailor interventions accordingly. Future research should assess whether interventions targeting these risk factors improve psychological outcome of COVID-19 patients and their relatives.

Supporting information

S1 File.
(DOCX)

S1 Data.
(XLSX)

Author Contributions

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Appendix B

Study II

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Psychological burden in patients with COVID-19 and their relatives 90 days after hospitalization: A prospective observational cohort study

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ABSTRACT

Objective: COVID-19 causes psychological distress for patients and their relatives at short term. However, little research addressed the longer-term psychological outcomes in this population. Therefore, we aimed to prospectively assess clinically relevant psychological distress in hospitalized patients with COVID-19 and their relatives 90 days after hospital discharge.

Methods: This exploratory, prospective, observational cohort study included consecutive adult patients hospitalized in two Swiss tertiary-care hospitals between March and June 2020 for confirmed COVID-19 and their relatives. The primary outcome was psychological distress defined as clinically relevant symptoms of anxiety and/or depression measured with the Hospital Anxiety and Depression Scale (HADS) 90 days after discharge.

Results: Clinically relevant psychological distress 90 days after hospital discharge was present in 23/108 patients (21.3%) and 22/120 relatives (18.3%). For patients, risk and protective factors associated with clinically relevant psychological distress included sociodemographic, illness-related, psychosocial, and hospital-related factors. A model including these factors showed good discrimination, with an area under the receiver-operating characteristic curve (AUC) of 0.84. For relatives, relevant risk factors were illness-related, psychosocial, and hospital-related factors. Resilience was negatively associated with anxiety and depression in both patients and relatives and regarding PTSD in relatives only.

Conclusion: COVID-19 is linked to clinically relevant psychological distress in a subgroup of patients and their relatives 90 days after hospitalization. If confirmed in an independent and larger patient cohort, knowledge about these potential risk and protective factors might help to develop preventive strategies.

1. Introduction

The novel Coronavirus disease 2019 (COVID-19) has caused a global pandemic with far-reaching consequences for many aspects of society, especially for patients diagnosed with COVID-19 and their relatives. While some patients have asymptomatic courses, many patients with COVID-19 experience a variety of symptoms or even develop an acute respiratory distress syndrome [1,2]. Especially vulnerable individuals,

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patients above 65 years, patients with obesity, and people with chronic lung disease or cardiovascular comorbidities [3,4], may experience severe disease courses, requiring intensive care treatment and being linked to increased risk for persisting impairments or even mortality [5–7]. In addition to somatic morbidity, COVID-19 may also cause severe psychological distress. In fact, research during previous similar epidemics has shown that patients are at high risk for mental disorders, including depressive and anxiety disorders, post-traumatic stress disorder (PTSD), and sleep disorders [8]. Further, during previous pandemics, isolation measures similar to the ones currently used to contain COVID-19 have been associated with adverse psychological effects on patients and relatives [9–12].

Still, for COVID-19, there is currently a lack of studies investigating longer-term psychological sequelae of the disease in patients and their relatives. There is growing evidence that COVID-19 is linked to short-term psychological outcomes in patients, relatives as well as the general population [13]. For instance, a large Swiss survey of the general public found an increase in the prevalence of depressive symptoms from 3.4% before the pandemic to 9.1% during confinement and 11.7% during partial deconfinement [14]. Further, studies found prevalence rates of around 50% for psychological morbidities such as depression or anxiety in COVID-19 survivors [13,15]. Again, these outcomes were caused by several factors including isolation of patients and relatives during the initial stage of hospitalization [16]. Still, longer-term psychological outcomes of COVID-19 patients and their relatives remain understudied.

Herein, our aim was to assess risk factors and prevalence of clinically relevant psychological distress in patients and their relatives 90 days after an index hospital stay of patients with COVID-19.

2. Materials and methods

2.1. Study setting

This exploratory, prospective observational two-center cohort study was conducted at the University Hospital Basel and the Kantonsspital Aarau, two tertiary care hospitals in Switzerland, from March until June 2020. The study was approved by the local Ethics Committee (Ethics Committee Northwest and Central Switzerland (Ethikkommission Nordwest- und Zentralschweiz, EKNZ); amendment to reference number 2019–01162). Written informed consent was provided by all participating patients and relatives. This manuscript adheres to the STROBE statement [17].

2.2. Study population

All patients consecutively admitted with COVID-19 and their closest relative were eligible for inclusion into this study. The criteria for hospitalization for COVID-19 were the overall clinical condition of the patient as well as clinical risk factors (e.g., age $>$ 65 years, respiratory rate $>$ 25/min, requirement of oxygen or pulmonary infiltrates observed on a chest imaging). Relatives were chosen according to surrogate decision-making rank (spouse $>$ parents/adult children $>$ others) as indicated in patients' medical records. Patients and relatives with insufficient knowledge of the local languages, cognitive impairment (i.e., a condition where patients were not able to understand and respond to the questions of our interview such as dementia or delirium), or serious psychiatric conditions (e.g., psychosis) were excluded. We did not apply any other exclusion criteria based on patient or COVID-19 related characteristics. We contacted patients and relatives by phone, informed them about our study and asked them to participate. To those who agreed, we sent a letter including the study information and informed consent form which they were asked to sign and return.

2.3. Collection of baseline and follow-up data of patients and relatives

For this study, we conducted telephone interviews with each patients and relatives 30 and 90 days after hospital discharge. In patients, we additionally reviewed medical charts and extracted clinical characteristics related to COVID-19. All other potential risk and protective factors were assessed at the 30-day "baseline" assessment. Primary and secondary outcomes, i.e., symptoms of anxiety, depression, and PTSD were assessed at the 90-day follow-up. To evaluate factors specific to the current pandemic, we used items designed for the purpose of this study. For all other predictive factors and all outcome variables, we conducted well-established clinical risk scores and validated psychometric measures.

2.3.1. Variables collected during hospitalization and baseline assessment 30 days after discharge

We collected potential predictor variables adhering to four domains, i.e., sociodemographic, illness-related, psychological, and hospital-related. Sociodemographic factors were the same for both samples, but factors in the other three domains partially differed to account for patient- and relative-specific characteristics.

Sociodemographic factors in both patients and relatives included age, gender, citizenship, cultural background, religious affiliation, civil status, children, and current job situation.

2.3.1.1. Patient variables and measures. In patients, illness-related factors included clinical parameters such as medication, i.e., investigational therapy, antibiotics, and anxiolytics during hospitalization, intensive care unit (ICU) stay, intubation, duration of hospitalization, and timepoint of COVID-19 diagnosis. Further, we assessed illness severity by the National Early Warning Score (NEWS) [18], a widely used tool to detect patients at risk of clinical deterioration, and severity of comorbidity by the Charlson Comorbidity Index (CCI) [19]. Self-perceived overall health status was evaluated with the visual analogue scale (VAS) of the EuroQol, ranging from 0 (worst imaginable health) to 100 (best imaginable health) [20,21]. In the domain of psychosocial factors, several psychological factors specific to the current pandemic were evaluated by items designed for the purpose of this study. In patients, these included worries caused by COVID-19 media reports, self-perceived stigma as well as a number of other potential concerning factors, i.e., worries about uncertain prognosis, burden of isolation measures, burden of boredom, worries about health of relatives, burden of missing relatives, worries about job situation, finances and medical care, and other worries as well as coping strategies, i.e., social contacts, distraction, tranquilizers and others. Patients rated each of these variables on a visual analogue scale (VAS) of 0–10. Additionally, we asked patients about pre-existing psychological comorbidities as well as frequency and kind of contact between them and their relatives.

Further, we assessed patients' perceived stress with the Perceived Stress Scale (10-item version; PSS-10), a widely-used tool to evaluate how unforeseeable, uncontrollable and overwhelming respondents perceived their life during the last 30 days. [22,23]. A study evaluating the psychometric properties of the PSS-10 in a representative sample of the German general population showed good internal consistency with a Cronbach alpha of 0.84 and good construct validity [24]. We determined resilience of patients through the 10-item version of the Connor-Davidson Resilience Scale (CD-RISC-10), indicating how well a person can cope with stress [25]. The CD-RISC is commonly used in clinical research and the original 25-item questionnaire as well as the 10-item version showed good validity with a Cronbach alpha of 0.89 and 0.88, respectively [25,26]. Further, the CD-RISC showed high test-retest reliability over a 12-month follow-up period [27–29]. Lastly, through items specifically designed for this study, we evaluated several hospital-related factors by a visual analogue scale of 0–10, i.e., perceived competence of treating physician, contradictory information given by

medical team, burden of having no visitors, missing physical closeness and asked patients if the psychosocial care team was involved.

2.3.1.2. Relative variables and measures. In relatives, in the domain of illness-related factors we assessed if they themselves were quarantined or infected with SARS-CoV-2, self-perceived overall health status (VAS of the EuroQol), the time point of the patient's COVID-19 diagnosis, as well if the patient had died. In alignment with patients' psychosocial variables, for relatives we also evaluated potential risk and protective factors related to the current pandemic evaluated by items designed for this study. Items rated on a VAS of 0–10 included worries and burdens, i.e., worries due to COVID-19 media reports, perceived overall burden due to COVID-19, worries about uncertain prognosis, worries about infection, burden of isolation measures, burden of separation from patient, and other worries as well as helpfulness of coping strategies, i.e., social contacts, distraction, tranquilizers, alcohol consumption, relaxation techniques, sports, and other coping strategies. Additionally, we asked relatives how they were related to the patient, if they lived in the same household, about the frequency of contact with patient, pre-existing psychological comorbidities, psychological help, and intake of psychotropic drugs. Further, we assessed perceived stress (PSS-10) and resilience (CD-RISC-10). Hospital-related factors included contact and satisfaction with the medical team, if the relative received information regarding prognosis, comprehensibility of medical information, if medical care was perceived as sufficient or inadequate, if the relative received recommendations regarding own care, if the psychosocial care team was involved, burden of not being able to visit the patient, and missing physical closeness.

2.3.2. Outcomes

Primary and secondary outcome for both patients and relatives were assessed at 90-day follow-up. The primary endpoint, psychological distress, defined as clinically relevant symptoms of anxiety and/or depression at the time of 90 days after discharge, was measured by the Hospital Anxiety and Depression Scale (HADS) [30]. This self-report measure was developed for patient populations hospitalized with medical conditions and does not contain items on physical symptoms to avoid somatic confounding. A review on psychometric properties of the HADS revealed good reliability and validity with a Cronbach's alpha of 0.83 and 0.82 for the subscales anxiety and depression, respectively, and an optimal balance between sensitivity and specificity of approximately 0.80 when applying a cut-off score of $\geq$8 on both subscales. In line with previous research, a score of $\geq$ 8 on the depression and/or anxiety subscale (range: 0–21) of the HADS, indicating clinically relevant symptoms of depression and/or anxiety, was defined as clinically relevant psychological distress for the purpose of our study [30,31].

The secondary outcome, i.e., symptoms of post-traumatic stress disorder, was assessed through a German translation of the Impact of Event Scale-revised (IES-R), which measures symptoms of emotional distress caused by traumatic events [32]. The IES-R is a 22-item questionnaire containing three subscales covering the three symptom domains intrusion, avoidance and hyperarousal. The IES-R has been shown to have high internal consistency with a Cronbach's alpha of 0.96 and good diagnostic accuracy when applying a cut-off score of 1.5 [33], which we used to categorize participants regarding symptoms of PTSD.

2.4. Statistical analyses

Descriptive statistics, i.e. frequencies as well as means and standard deviations were used to present characteristics of the study population. Data from the patient and relative sample were analyzed separately. To investigate the associations of potential risk and protective factors assessed at 30-day follow-up and clinically relevant psychological distress at 90-day follow-up, we conducted univariable logistic regression models. We further conducted multivariable logistic regression models within the four domains, each including all significantly associated variables of the respective domain as well as the pre-defined variables age and gender in the patient sample and age, gender and death of patient in the relative sample. To investigate which variables might be independently associated, we additionally calculated a combined regression model including the pre-defined as well as all risk and protective factors associated with the outcome in univariable analyses. We show odds ratios (OR) and 95% confidence intervals (CI) as a measure of association and the area under the receiver operating characteristic curve (AUC) as a measure of discrimination. A p-value of $<$ 0.05 (two-tailed) was considered statistically significant. All statistical analyses were conducted using Stata 15 (Stata Corp, College Station, Texas, USA).

3. Results

3.1. Study sample and baseline demographics

Between March and June 2020, 301 patients with COVID-19 were hospitalized at the University Hospital of Basel (n = 198) and Kantonsspital Aarau (n = 103). Fig. 1 shows the flowchart of patients and relatives regarding study inclusion. Forty patients (13.3%) had died until 30-day follow-up assessment, 86 (28.9%) met exclusion criteria such as insufficient knowledge of the local language (17.9%), cognitive impairment or severe underlying psychiatric conditions (10.6%), 47 (15.6%) were not reachable by phone and 20 (6.6%) did not give informed consent. Twelve (4%) patients did not indicate any relatives. Of the 289 remaining relatives, 15.9% did not speak the local language and 8.3% did not give informed consent. Seventy-eight (27%) of eligible relatives were not reachable by phone for the either the 30- or 90-day assessment. The final samples therefore consisted of 108 patients and 120 relatives.

Sociodemographic and clinical characteristics of the patient and relative cohorts are shown in Table 1. Patients were on average 58 years old and 41.1% were female. The mean duration of hospitalization was 9 days and 18 (16.8%) patients were transferred to the ICU with 11 (10.4%) requiring intubation. Relatives' mean age was 58 years, 79% were female, and they were mainly patients' spouses (52.1%).

3.2. Primary endpoint of patients: clinically relevant psychological distress 90 days after discharge

First, we focused on the patient cohort. Twenty-three patients (21.3%) showed clinically relevant psychological distress, i.e., symptoms of depression and/or anxiety defined by a score of $\geq$8 on the depression and/or anxiety subscale of the HADS. Of those, 20 (18.5%) showed symptoms of anxiety and ten (9.3%) symptoms of depression, with seven patients (6.5%) showing both.

Several factors were associated with clinically relevant psychological distress in univariable analyses (see Supplemental Table S1), including sociodemographic, i.e., female gender, illness-related, i.e., lower perceived health status, psychosocial, i.e., lower resilience, higher level of perceived stress, increased worries due to COVID-19 media reports, worries by isolation measures, burden by boredom, worries about job situation, worries about medical care, and hospital-related factors, i.e., burden of having no visitors and missing physical contact. The psychosocial domain model yielded an AUC of 0.82, the highest AUC of all domain models which is only slightly lower than the AUC of the overall model (Table 2).

3.3. Primary endpoint of relatives: clinically relevant psychological distress 90 days after discharge

Second, we focused on the cohort of relatives. Twenty-two relatives (18.3%) showed clinically relevant psychological distress, i.e., symptoms of depression and/or anxiety 90 days after patients' discharge. Of

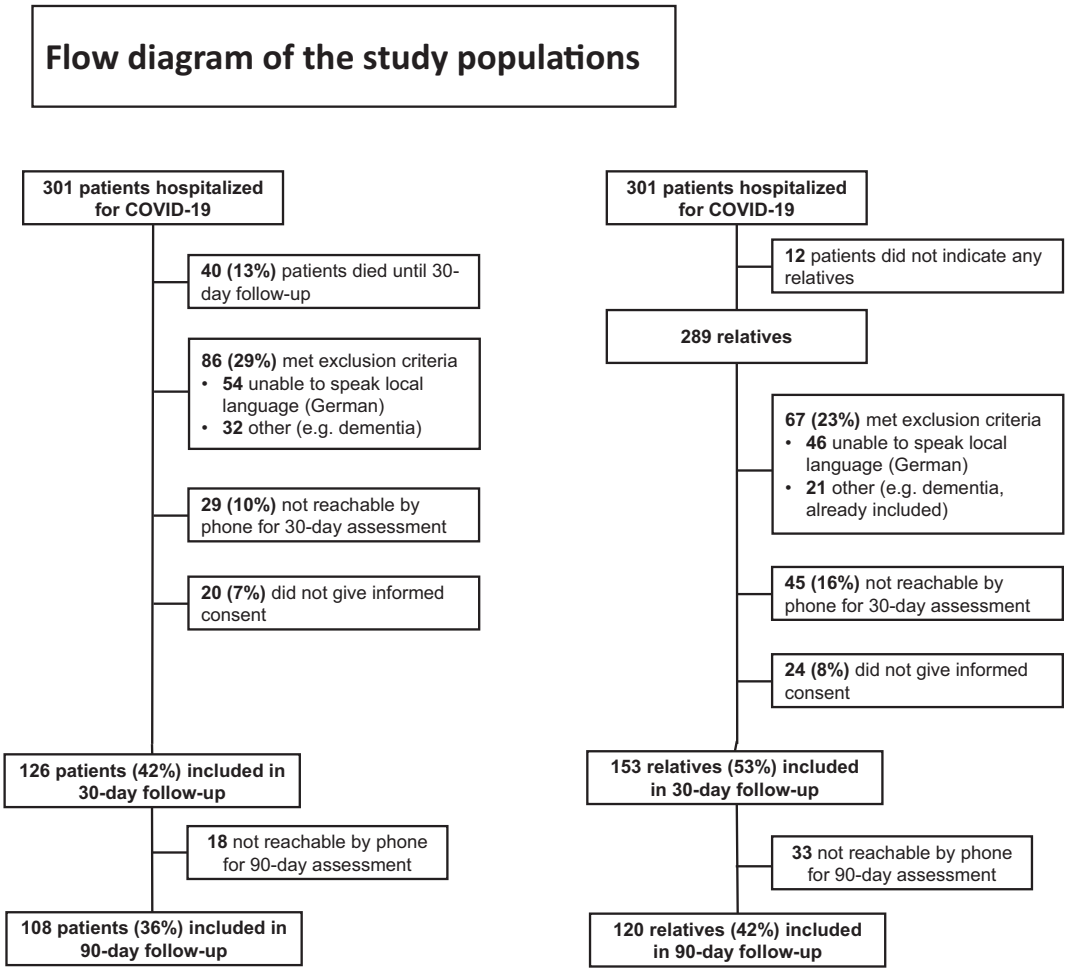

Fig. 1. Flow diagram of the study population.
Flow diagram illustrating inclusion and exclusion of eligible participants.

those, 17 (14.2%) relatives displayed symptoms of anxiety and 13 (10.8%) symptoms of depression with eight relatives (6.7%) having both.

Several factors were associated with clinically relevant psychological distress in univariable analyses, including illness-related, i.e., lower perceived health status, psychosocial, i.e., lower resilience, higher level of perceived stress, type of communication between relatives and patients, higher perceived overall burden, increased worries due to uncertain prognosis, higher burden of isolation measures, helpfulness of sport and other coping strategies, and hospital-related factors, i.e., higher burden due to not being able to visit the patient and missing physical closeness (see Supplemental Table S2). Self-perceived overall health status, perceived stress, perceived overall burden due to COVID-19, and sport as a helpful coping strategy were independently associated with clinically relevant psychological distress within the four domain models (Table 3). The psychosocial domain model showed the same discriminative value as the overall multivariable model with an AUC of 0.95.

3.4. Secondary endpoints: PTSD in patients and relatives 90 days after discharge

Third, we focused on PTSD in the patient and the relative cohorts as a secondary outcome. A total of 8 patients (7.8%) showed symptoms of PTSD. In univariable analyses, factors that were associated with symptoms of PTSD in patients were sociodemographic factors, i.e., female gender, non-central/western European background, being widowed, separated or single, illness-related factors, i.e., lower perceived health status, and psychosocial factors, i.e., higher perceived stress, increased worries due to COVID-19 media reports, and being worried about job situation or finances (see Supplemental Table S3). Cultural background and civil status were independently associated within the sociodemographic domain. The sociodemographic and psychosocial model each yielded an AUC of 0.86 while the overall multivariable model including all statistically significant variables as well as age and gender showed an AUC of 0.69 (Table 4).

Eight of the 113 relatives (7.1%) with available information suffered from considerable PTSD symptoms. Illness-related, i.e., lower perceived health status, psychosocial, i.e., intake of psychotropic drugs, lower resilience, higher perceived stress, increased worries due to COVID-19 media reports, and higher burden of isolation measures and hospital-related factors, i.e., not being able to visit the patient were associated with relatives' PTSD symptoms (see Supplemental Table S4). Resilience emerged as an independently associated factor within the psychosocial domain. The psychosocial domain model and the overall multivariable model showed an AUC of 0.95 (Table 5).

4. Discussion

Within this two-center, exploratory, prospective observational cohort study assessing the prevalence of clinically relevant psychological distress and associated factors in patients with COVID-19 and their relatives 90 days after hospitalization, we found that a quarter of patients and relatives suffered from psychological distress 90 days after

Table 1
Sociodemographic and clinical characteristics of the study populations.

Characteristics	Patients	Relatives
	$n = 108$	$n = 120$
Age, years	58.4 (15.8)	57.6 (14.7)
<40 years	12 (11.2%)	13 (10.9%)
40–64 years	56 (52.3%)	66 (55.5%)
65–80 years	33 (30.8%)	31 (26.1%)
>80 years	6 (5.6%)	9 (7.6%)
Gender, female	44 (41.1%)	94 (79.0%)
Citizenship		
Switzerland	73 (68.9%)	99 (83.2%)
Germany	14 (13.2%)	5 (4.2%)
France	5 (4.7%)	6 (5.0%)
Other	14 (13.2%)	9 (7.6%)
Cultural background		
Central Europe	78 (73.6%)	90 (75.6%)
Western Europe	7 (6.6%)	7 (5.9%)
Eastern Europe	4 (3.8%)	6 (5.0%)
Southern Europe	7 (6.6%)	9 (7.6%)
Northern Europe	2 (1.9%)	0
Asia	1 (0.9%)	0
Africa	4 (3.8%)	0
Religious affiliation		
Catholic	28 (26.7%)	35 (29.4%)
Protestant	25 (23.8%)	39 (32.8%)
Other Christian denomination	6 (5.7%)	9 (7.6%)
Jewish	2 (1.9%)	2 (1.7%)
Muslim	8 (7.6%)	5 (4.2%)
Other religion	2 (1.9%)	3 (2.5%)
No religious affiliation	34 (32.4%)	26 (21.8%)
Civil status		
Married/in partnership	67 (63.2%)	92 (77.3%)
Divorced	19 (17.9%)	9 (7.6%)
Widowed	6 (5.7%)	6 (5.0%)
Single	14 (13.2%)	12 (10.1%)
Children, yes	71 (69.6%)	88 (73.9%)
Education		
High School	9 (8.8%)	4 (3.4%)
Apprenticeship	70 (68.6%)	76 (64.4%)
College/University	23 (22.5%)	38 (32.2%)
Current job situation		
Employed	63 (60.0%)	57 (50.0%)
Unemployed	0	4 (3.5%)
Retired	37 (35.2%)	43 (37.7%)
Disability benefits	2 (1.9%)	3 (2.6%)
Homemaker	2 (1.9%)	5 (4.4%)
Other	1 (1.0%)	2 (1.8%)
Previous psychotherapy	6 (5.8%)	8 (7.1%)
Pre-existing psychological comorbidities	15 (14.6%)	14 (12.6%)
Follow-up duration: hospital discharge to 30 day-assessment, days	33.6 (5.7)	36.8 (7.5)
Follow-up duration: 30- to 90 day-assessment, days	66.3 (14.4)	61.7 (13.1)
Patient characteristics		
Duration of hospitalization (days), mean (SD)	8.95 (6.63)	
Severity of illness (NEWS score), mean (SD)	6.16 (3.58)	
Comorbidity (CCI), mean (SD)	2.36 (2.09)	
Antibiotics during hospitalization	36 (34.3%)	
Oxygen supply		
No oxygen supply	39 (36.8%)	
Nasal cannula/NIV	56 (52.8%)	
Intubation	11 (10.4%)	
Anxiolytics during hospitalization	20 (19.2%)	
Investigational treatment[a]	74 (70.5%)	
ICU stay (yes/no)	18 (16.8%)	
Relatives' characteristics		
Relationship to patient		
Patient is spouse		62 (52.1%)
Patient is child		7 (5.9%)
Patient is sibling		11 (9.2%)
Patient is parent		27 (22.7%)
Other		12 (10.1%)
Relative living in same household with patient		64 (53.8%)
Relative quarantined		46 (44.2%)
Relative also infected with COVID-19		37 (32.7%)

Data are presented as n (%) or mean (standard deviation).
Abbreviations: SD, standard deviation; NEWS, National Early Warning Score; NIV, Non-invasive ventilation; ICU, Intensive Care Unit; CCI, Charlson Comorbidity Index;
[a] Investigational treatment: Hydroxychloroquine, Lopinavir/Ritonavir, Remdesivir, Tocilizumab, Convalescent Plasma.

hospital discharge. Several sociodemographic, illness-related, psychosocial and hospital-related risk factors and protective factors associated with clinically relevant psychological distress in patients and relatives were identified with each only moderate discrimination in ROC analyses and few independently associated. When combining all psychosocial factors that showed a statistically significant association, however, there was high prognostic accuracy to identify these patients and relatives. The same was true for the combination of age and gender and the significantly associated factors from all four domains in patients, as well as age, gender, death of patient and the significantly associated factors from all four domains in relatives. This is a relevant finding, because some of the factors may be at least partially modifiable during routine hospital care.

Several points of our results are worth discussing. First, the rates of clinically relevant psychological distress found in this study are in line with findings from recent short-term follow-up studies: Early studies on the psychological consequences of COVID-19 showed prevalence rates among newly recovered patients from 14% and 11% to 21% and 29% of anxiety and depression symptoms, respectively [34,35]. Mazza et al. evaluated Italian adults surviving COVID-19 one month after hospital discharge of which 31% reported clinically relevant depression and 42% anxiety symptoms [15]. In our follow-up, we found 21.3% of patients and 18.3% of relatives suffering from clinically relevant psychological distress. These short-term findings are comparable with our findings at

Table 2
Multivariable associations of predictor variables and clinically relevant psychological distress at 90-day follow-up in patients.

	Multivariable models within domains			Overall multivariable model, adjusted for age & gender	
	OR (95% CI)	*p*	AUC	OR (95% CI)	*p*
Sociodemographic factors					
Age (years)	0.98 (0.95, 1.01)	0.227	0.67	1.01 (0.97, 1.06)	0.653
Gender (female)	3.51 (1.32, 9.3)	**0.012**		1.59 (0.49, 5.16)	0.438
Illness-related factors					
Self-perceived overall health status (Euroqol VAS 0–100), mean (SD)	0.97 (0.94, 0.99)	**0.014**	0.63	0.98 (0.94, 1.01)	0.215
Psychosocial factors					
Resilience (CD-RISC), mean (SD)	0.92 (0.83, 1.03)	0.140	0.82	0.92 (0.83, 1.03)	0.154
Perceived Stress (PSS-10), mean (SD)	1.09 (0.99, 1.2)	0.068		1.09 (0.98, 1.21)	0.126
Worries due to COVID-19 media reports, mean (SD)	1.19 (0.98, 1.44)	0.085		1.17 (0.96, 1.42)	0.131
Burden of isolation measures, mean (SD)	1.02 (0.85, 1.23)	0.841		1.03 (0.8, 1.33)	0.825
Burden of boredom, mean (SD)	1.06 (0.89, 1.26)	0.500		1.08 (0.9, 1.3)	0.389
Worried about job situation, mean (SD)	1.02 (0.84, 1.23)	0.880		1.03 (0.81, 1.29)	0.831
Worried about medical care, mean (SD)	1.33 (0.96, 1.86)	0.089		1.35 (0.94, 1.95)	0.107
Hospital-related factors (VAS 0–10)					
Burden of having no visitors, mean (SD)	1.13 (0.91, 1.4)	0.264	0.66	0.92 (0.67, 1.27)	0.621
Missing physical contact/ closeness, mean (SD)	1.06 (0.86, 1.3)	0.604		1.04 (0.8, 1.35)	0.783

Note. SD, standard deviation; OR, odds ratio; 95%CI, 95% Confidence Interval; COVID-19, Coronavirus disease 2019; CD-RISC, Connor-Davidson Resilience Scale; PSS-10, Perceived Stress Scale; VAS, visual analogue scale. *P*-values < 0.05 were considered statistically significant.

Table 3
Multivariable associations of predictor variables and psychological distress at 90-day follow-up in relatives.

	Multivariable model within domains			Overall multivariable model, adjusted for age & gender	
	OR (95% CI)	*p*	AUC	OR (95% CI)	*p*
Socio-demographic factors					
Age (years)	1.01 (0.98, 1.04)	0.656	0.55	1.02 (0.97, 1.07)	0.501
Gender (female)	1.82 (0.49, 6.76)	0.368		0.54 (0.06, 4.88)	0.587
Illness-related factors					
Self-perceived overall health status (Euroqol VAS 0–100), mean (SD)	0.93 (0.9, 0.96)	**<0.001**	0.78	0.96 (0.91, 1.01)	0.142
Death of patient	2.12 (0.54, 8.25)	0.280		0.94 (0.05, 19.05)	0.968
Psychosocial factors					
Resilience (CD-RISC), mean (SD)	0.87 (0.74, 1.03)	0.113	0.95	0.87 (0.72, 1.06)	0.163
Perceived Stress (PSS), mean (SD)	1.25 (1.04, 1.51)	**0.020**		1.22 (1.00, 1.50)	0.052
Type of communication between relatives and patients					
Telephone, text and other	1 (Ref)			1 (Ref)	
Video calls & visits	0.56 (0.10, 3.02)	0.501		0.83 (0.11, 6.07)	0.853
Burdening factors (VAS 0–10)					
Perceived overall burden, mean (SD)	1.86 (1.22, 2.82)	**0.004**		1.77 (1.13, 2.76)	**0.012**
Worries by uncertain prognosis, mean (SD)	0.92 (0.73, 1.16)	0.495		0.88 (0.68, 1.15)	0.353
Burden of isolation measures, mean (SD)	0.86 (0.66, 1.13)	0.282		0.84 (0.63, 1.12)	0.245
Helpfulness of coping strategies (VAS 0–10)					
Sport, mean (SD)	0.80 (0.64, 1.00)	**0.047**		0.86 (0.67, 1.11)	0.249
Other, mean (SD)	0.91 (0.75, 1.10)	0.304		0.92 (0.74, 1.15)	0.462
Hospital-related factors (VAS 0–10)					
Burden of not being able to visit patient (VAS 0–10), mean (SD)	1.15 (0.93, 1.43)	0.198	0.76	1.05 (0.67, 1.65)	0.821
Missing physical contact/ closeness (VAS 0–10), mean (SD)	1.2 (0.99, 1.45)	0.064		1.18 (0.85, 1.64)	0.329

Note. SD, standard deviation; OR, odds ratio; 95%CI, 95% Confidence Interval; CD-RISC, Connor-Davidson Resilience Scale; PSS-10, Perceived Stress Scale; VAS, visual analogue scale. *P*-values < 0.05 were considered statistically significant.

three-months follow-up, which highlights the need to reduce these sequelae by better caring for patients and relatives [36]. Herein, we identified several potential targets. Whether preventive strategies help to reduce these risks, however, remains unclear and needs further research.

Interestingly, in our study the proportion of patients and relatives with clinically relevant psychological distress was similar to the proportion of patients reporting symptoms of anxiety. This is in line with a recent study reporting also high levels of anxiety and depression in both, isolated patients with COVID-19 and their relatives, during the initial stage of hospitalization [16]. Anxiety was also predominant in their analysis. Similarly, also other studies investigating relatives of patients with COVID-19 or other infections in the context of previous epidemics suggest that they suffer from higher levels of distress as compared to individuals of the general population [35,37–41]. Importantly, we have learned that also the non-infected Swiss general population have an increase in depressive symptoms to up to 11.7% [14]. This suggests, that even though the pandemic has taken a toll on the mental well-being of all [39–41], more attention should be paid to patients with COVID-19 and their relatives in order to develop strategies to prevent persistent adverse psychological outcomes [38,42,43].

Several potential risk and protective factors could be identified in this study, although not all of them are modifiable, but still may help to

Table 4
Multivariable associations of predictor variables and PTSD symptoms at 90-day follow-up in patients.

	Multivariable models within domains			Overall multivariable model, adjusted for age & gender	
	OR (95% CI)	*p*	AUC	OR (95% CI)	*p*
Sociodemographic factors					
Age (years)	0.99 (0.94, 1.04)	0.761	0.86	1.05 (0.96, 1.15)	0.297
Gender (female)	5.84 (0.73, 46.58)	0.096		2.89 (0.09, 91.82)	0.548
Cultural background					
Central/Western Europe	1 (Ref)			1 (Ref)	
Other	13.82 (1.33, 143.3)	**0.028**		20.82 (0.18, 2473.88)	0.213
Civil status					
Married/partnership	1 (Ref)			1 (Ref)	
Widowed/separated/ single	7.09 (0.98, 51.36)	0.052		34.08 (0.36, 3209.94)	0.128
Illness-related factors					
Self-perceived overall health status (Euroqol VAS 0–100), mean (SD)	0.95 (0.91, 1.00)	**0.030**	0.65	1.01 (0.95, 1.08)	0.695
Psychosocial factors					
Perceived Stress (PSS-10), mean (SD)	1.14 (0.99, 1.31)	0.072	0.86	1.12 (0.90, 1.39)	0.328
Worries due to COVID-19 media reports, mean (SD)	1.37 (0.97, 1.91)	0.070		1.39 (0.89, 2.18)	0.146
Worried about job situation, mean (SD)	1.02 (0.71, 1.46)	0.915		1.29 (0.75, 2.20)	0.360
Worried about finances, mean (SD)	1.45 (0.98, 2.13)	0.060		1.25 (0.77, 2.04)	0.369

Note. SD, standard deviation; COVID-19, Coronavirus disease 2019; PSS, Perceived Stress Scale; VAS, Visual Analogue Scale. *P*-values < 0.05 were considered statistically significant.

Table 5
Multivariable associations of predictor variables and PTSD symptoms at 90-day follow-up in relatives.

	Multivariable models within domains			Overall multivariable model, adjusted for age & gender	
	OR (95% CI)	*p*	AUC	OR (95% CI)	*p*
Sociodemographic factors					
Age (years)	0.98 (0.93, 1.03)	0.408	0.58	0.98 (0.91, 1.05)	0.602
Illness-related factors					
Self-perceived overall health status (VAS 0–100), mean (SD)	0.95 (0.91, 0.99)	**0.009**	0.78	0.99 (0.93, 1.06)	0.864
Psychosocial factors					
Psychotropic drugs	2.65 (0.20, 34.87)	0.459	0.95	2.95 (0.20, 43.04)	0.429
Resilience (CD-RISC), mean (SD)	0.77 (0.61, 0.97)	**0.024**		0.78 (0.62, 0.97)	**0.027**
Perceived Stress (PSS), mean (SD)	1.11 (0.94, 1.32)	0.218		1.09 (0.88, 1.36)	0.429
Worried due to COVID-19 media reports, mean (SD)	1.71 (0.90, 3.24)	0.099		1.70 (0.81, 3.56)	0.161
Burden of isolation measures, mean (SD)	1.20 (0.81, 1.79)	0.353		1.23 (0.79, 1.92)	0.367
Hospital-related factors					
Burden of not being able to visit patient (VAS 0–10), mean (SD)	1.46 (1.03, 2.09)	0.035	0.76	1.00 (0.57, 1.76)	0.995

Note. SD, standard deviation; COVID-19, Coronavirus disease 2019; CD-RISC, Connor-Davidson Resilience Scale; PSS, Perceived Stress Scale; VAS, Visual Analogue Scale. *P*-values < 0.05 were considered statistically significant.

identify high risk subjects. Some of these factors are known to be associated with psychological distress in general such as female gender, subjective health and resilience, while other factors such as the burden due to isolation measures or COVID-19 media reports are specific to the current pandemic.

Regarding the former category, we found that female patients were significantly more likely than males to suffer from clinically relevant psychological distress. In the general population, women are known to be more prone to depression and anxiety disorders [44]. Previous research also reported increased risk for anxiety and depression in women affected by COVID-19 [15,16,45]. Interestingly, gender of relatives and being in a relationship were not associated with psychological distress in relatives in our sample. Possibly, the current pandemic poses specific challenges on these relationships. Social support is a well-known protective factor regarding mental health, which has been affected by contact restrictions in COVID-19 patients. A review on the effects of quarantine measures during previous epidemics indicated a negative impact on psychological well-being of patients and relatives especially due to separation from partners and relatives [9], which is in line with the findings of our study. While the majority of women tend to feel most emotionally supported by their friends, men usually report to mainly turn to their partner for emotional support [46,47]. Thus, particularly male relatives may experience distress due to fear about the course of disease of the partner and the lack of emotional support. Still, further research re-evaluating our findings and conducting external validation of prediction models is needed. Also, rates of psychological distress often decline with increasing age overall [48], and in COVID-19 [37,49]. Still, there was no association of age and distress in our sample. As we focused our study to older, hospitalized patients, our study might have been biased in this regard.

Within the domain of illness-related factors, patients and relatives with lower subjective overall health status experienced increased psychological distress. Objective clinical parameters usually concomitant with psychological sequelae, e.g., high illness severity and hospitalization in the ICU [50–52], however, were not associated. This might potentially be explained by the comparably small number of patients with severe illness course who needed intensive care treatment, i.e. 18 patients (16%) in our sample vs. 26% in a recent meta-analysis [53]. Several psychosocial factors were associated with clinically relevant psychological distress as expected and a combination of those showed high predictive value. Resilience, which can be defined as a person's emotional and mental capacity to adapt well when experiencing critical life events [54–56], was negatively associated with anxiety and depression in both patients and relatives and with PTSD in relatives only. Resilience was not independently associated though and its association might be explained by other psychosocial characteristics and circumstances. Based on our findings, availability of coping strategies such as exercise or social support through telephone and video calls as well as risk factors such as perceived stress or the overall burden due to COVID-19 might mediate the association between resilience and symptoms of anxiety, depression and PTSD. There is evidence indicating that resilience might be associated with poor mental health, e.g.,

symptoms of depression and anxiety in general [57]. Further, a review on resilience as a protective factor regarding symptoms of anxiety, depression and post-traumatic stress during the current pandemic found that many people use "resilient" coping strategies to handle COVID-19-related distress [58]. Exercise, which has a well-known positive effect on symptoms of depression and anxiety, emerged as a helpful coping strategy in relatives in our study. Perceived stress, a widely-researched risk factor for symptoms of anxiety, depression and PTSD was associated with clinically relevant psychological distress in both patients and relatives. Future studies are needed to better understand how these factors are connected.

Further, we identified several potential risk and protective factors specific to COVID-19 that were associated with clinically relevant psychological distress in patients and relatives. Similar to other studies, overall burden due to COVID-19 was a relevant factor [14]. In addition, social connectedness did not significantly affect psychological distress in multivariable analyses beyond other psychosocial factors and its effect might therefore significantly vary depending on other characteristics and circumstances. The perceived burden of isolation measures, the burden of having no visitors or not being able to visit and missing physical contact were associated with clinically relevant psychological distress in patients and relatives. This again is in line with older studies showing adverse psychological effects of quarantine and isolation [9,16,37]. Particularly, physical distancing seems to be an important factor for psychological distress [59]. Bridging this gap between physical distancing and social connection might be possible with the help of digital technologies and more such interventions are urgently needed. However, our findings suggest that social connectedness may be considered in a larger context of several relevant interacting psychosocial factors.

Overall, of the factors associated with clinically relevant distress in our study, many are well-known risk and protective factors and some are specific to COVID-19. This emphasizes the importance of not solely focusing on the negative impact of the COVID-19 pandemic and associated restrictions specifically but additionally considering the known characteristics that pose individuals at increased risk of developing significant psychological distress as well as the known protective factors and interventions that buffer the negative impact of stressful life events. Future research should further evaluate the role and interactions of known predictive factors and potential COVID-19 related risk factors. Insight into these dynamics might help to identify individuals who are at increased risk early on and to provide adequate support with the aim to prevent or mitigate mental health problems. Considering PTSD, one short-term follow-up study found a majority of inpatients with COVID-19 to report PTSD symptoms [60], while another found a third of patients showing clinically relevant symptoms [15]. In our population, the lower rates of 7.8% and 7.1% for PTSD symptoms in patients and relatives, respectively, might be reflected by the later timepoint of our assessment. The higher rates found in the other studies [15,60] might therefore display symptoms of acute stress remitting within 1 month after a traumatic event, of which only a minority develop a full PTSD [61].

4.1. Limitations

This study has some limitations. This two-center Swiss study was rather small and did not allow for rigorous statistical adjustment. Also, the observational design does not allow to draw any conclusions regarding preventive effects and the study is thus rather hypothesis generating. Due to the limited sample size, we did not have separate derivation and validation samples. External validation in independent and larger cohorts is therefore warranted. Further, the follow-up period of 3 months may have led to other factors leading to psychological distress and may confound findings as we did not have an unaffected control cohort at hand. Further, as the aim of this study was to assess a broad scope of potential risk and protective factors, multiple tests were conducted without statistical correction, to aid in an exploratory hypothesis generation. However, a type I error cannot be ruled out and findings must, therefore, be considered exploratory and need validation.

4.2. Conclusions

A quarter of hospitalized patients with COVID-19 and their relatives experience clinically relevant psychological distress 90 days after hospital discharge. Psychosocial and isolation-related factors associated with psychological distress are at least partially modifiable during routine hospital care. External validation of these exploratory findings in a larger patient cohort is warranted.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2021.110526.

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Appendix C

Study III

Vincent, A., Beck, K., Thommen, E., Widmer, M., Becker, C., Loretz, N., Gross, S., Mueller, J., Amacher, S.A., Bohren, C., Schaefert, R., Gaab, J., Marsch, S., Emsden, C., Tisljar, K., Sutter, R., Hunziker, S. (2022). Post-intensive care syndrome in out-of-hospital cardiac arrest patients: A prospective observational cohort study. *PLoS ONE, 17*(10), e0276011. *https://doi.org/10.1371/journal.pone.0276011*

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RESEARCH ARTICLE

Post-intensive care syndrome in out-of-hospital cardiac arrest patients: A prospective observational cohort study

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Abstract

Introduction

Intensive care unit patients are at risk for post-intensive care syndrome (PICS), which includes psychological, physical and/or cognitive sequelae after their hospital stay. Our aim was to investigate PICS in adult patients with out-of-hospital cardiac arrest (OHCA).

Methods

In this prospective observational cohort study, we assessed risks for PICS at 3 and 12-month follow-up within the following domains: a) physical impairment (EuroQol [EQ-5D-3L]), b) cognitive functioning (Cerebral Performance Category [CPC] score >1, modified Rankin Scale [mRS] >2) and c) psychological burden (Hospital Anxiety and Depression Scale [HADS], Impact of Event Scale-Revised [IES-R]).

Results

At 3 months, 69/139 patients (50%) met the definition of PICS including 37% in the physical domain, 25% in the cognitive domain and 13% in the psychological domain. Intubation (OR 2.3, 95%CI 1.1 to 5,0 p = 0.03), sedatives (OR 3.4, 95%CI 1 to 11, p = 0.045), mRS at discharge (OR 4.3, 95%CI 1.70 to 11.01, p = 0.002), CPC at discharge (OR 3.3, 95%CI 1.4 to 7.6, p = 0.005) and post-discharge work loss (OR 13.4, 95%CI 1.7 to 107.5, p = 0.014) were significantly associated with PICS. At 12 months, 52/110 (47%) patients had PICS, which was associated with prolonged duration of rehabilitation, higher APACHE scores, and higher mRS and CPC scores at hospital discharge.

Competing interests: The authors have declared that no competing interests exist.

Conclusions

Nearly half of long-term OHCA survivors show PICS after 3 and 12 months. These high numbers call for more emphasis on appropriate screening and treatment in this patient population. Future studies should evaluate whether early identification of these patients enables preventive strategies and treatment options.

Introduction

Out-of-hospital cardiac arrest (OHCA) remains an important cause of death worldwide [1]. Less than a quarter of OHCA patients survive to hospital admission, and only half of initial survivors are discharged from the hospital alive [2]. Although therapeutic advances in intensive care medicine result in a higher number of ICU survivors, the overall ICU mortality decreased only very slightly over time due to the steadily increase of patients' age and the number of comorbidities upon ICU admission [3]. Also, the risk of severe neurological deficits in ICU patients remains high [4,5] particularly in survivors of an out-of-hospital cardiac arrest (OHCA). In consequence, long-term physical, neurological and mental health status of ICU survivors has become an increasing concern in recent years [6]. These long-term impairments have been summarized under the term post-intensive care syndrome (PICS), which is commonly defined as new or aggravated dysfunction(s) in the physical, cognitive and/or mental (psychiatric) domain after critical illness [7]. Several studies suggest that more than 50% of ICU survivors suffer from at least one component of PICS [6,8]. Accordingly, PICS is becoming a more widely used concept in current clinical practice, even though attempts to define it with clinical accuracy are still ongoing [9].

Importantly, there is insufficient research data regarding the risk for PICS in the population of OHCA patients, although this population of patients is clearly at increased risk to suffer from long-term impairments and have worse physical and social functioning compared to the general population [10]. Studies have suggested that a relevant number of OHCA patients have moderate disabilities, poor autonomy and cognitive impairments particularly in regard to memory, attention and executive functioning [10–14]. In addition, OHCA patients are at increased risk for symptoms of depression, anxiety and posttraumatic stress disorder (PTSD) [15,16]. There are several well-known risk factors for adverse long-term health after OHCA including low-flow time, clinical severity at ICU admission, prolonged coma duration, and mechanical ventilation [11]. Also, young age and female gender was associated with higher risk for poor health [12].

Yet, to the best of our knowledge, only few studies have addressed the concept of PICS in OHCA patients. Better understanding the risk of PICS in OHCA patients is important for adequate future screening and treatment of patients at risk and may help to prevent PICS. Herein, we investigated the prevalence and potential risk factors for PICS in a well-defined cohort of adult OHCA survivors among the domains of physical, cognitive and psychological symptoms.

Materials and methods

Study setting

The COMMUNICATE study is an ongoing prospective observational cohort study (from 10/2012 to 10/2025) at ICU of the University Hospital Basel, a Swiss tertiary care hospital with

ongoing sampling. The aim of the trial is to investigate the prognosis and long-term outcomes in consecutive adult patients after cardiac arrest. The methods applied in this study have been published previously [17–19]. The COMMUNICATE trial was approved by the local Ethics Committee (Ethics Committee Northwest and Central Switzerland, EKNZ; approval reference number: 2019–01162) and is conducted in accordance with the declaration of Helsinki. All patients, or in case of unconsciousness, patients' next of kin provided written informed consent for study participation.

Study population

We included adult patients after OHCA who were admitted to the ICU and who participated in the 3-month and/or 12-month follow-up assessment after hospital/ICU admission. Further, we also included patients with in-hospital cardiac arrest (IHCA) if these were not monitored and had thus a similar risk for adverse outcome compared to OHCA patients. No exclusion criteria regarding patient characteristics, e.g., consciousness, type, severity, or duration of cardiac arrest were used.

Data collection

Data were prospectively collected upon ICU admission. Patients' medical characteristics were extracted from hospital medical records. Further, we conducted predefined and structured telephone interviews with patients 3 and 12 months after ICU admission to evaluate outcomes. To assess outcomes, the research team performed systematic telephone interviews with patients lasting for around 20 minutes. Thereby, questionnaires were read aloud and patients' answers were recorded.

Measures

Baseline predictor variables. We calculated all clinical scores at ICU arrival as suggested in original publications [20,21]. From hospital medical records, we collected patients' sociodemographic information (e.g., age, gender, working status), the setting of cardiac arrest (e.g., location, initial rhythm, no-flow time, low-flow time), adrenaline (epinephrine) dose given), the reason for OHCA (i.e., coronary heart disease, arrhythmogenic, other reason), the ICU treatment received (e.g., intubation, targeted temperature management, use of vasoactive or sedative medication), medical complications during ICU stay (e.g., delirium), comorbidities (e.g., smoking status, hyperlipidemia, coronary disease, diabetes, renal failure, malignant disease), and ICU and hospital length of stay. Further, we assessed the number of weeks in rehabilitation and working status three months after hospitalization.

Outcome measures. All outcome measures were assessed at 3-month and 12-month follow-up. The primary outcome PICS was defined as symptoms or impairment in at least one of the following domains, as previously defined [7]: physical impairment, cognitive impairment and/or psychological distress. The primary endpoint was PICS measured at 3 months and secondary endpoint was PICS at 12 months follow-up.

Physical impairment. Physical impairment was evaluated with the EuroQol questionnaire (EQ-5D-3L), an established, extensively validated, as well as time-efficient self-report measure which assesses general health-related quality of life [22]. The EQ-5D-3L comprises five dimensions, i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression, which can be rated on three levels, i.e. no problems, some problems and extreme problems. These dimensions can be summarized in an index ranging from -0.5 "worse than death" to 1 "full health" [23]. We used a cut-off score of $\leq$0.8 to determine relevant physical impairment. Cronbach's alpha for this sample was $\alpha = 0.65$.

Cognitive impairment. To assess cognitive impairment, we used the Cerebral Performance Category (CPC) [24] and the modified Rankin Scale (mRS) [25], two expert-rated and time-efficient scales.

The CPC measures patients' neurological status. It distinguishes five levels. In line with previous studies, we defined level 1 (good recovery) as favorable neurological outcome, and 2 (moderate disability), 3 (severe disability), 4 (vegetative state) and 5 (death) as poor neurological outcome [26].

The mRS scale assesses neurological function on a scale from 0 to 6. We defined levels 0 (no symptoms), 1 (no significant disability despite symptoms; able to carry out all usual duties and activities) and 2 (slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance) as favorable outcome; and levels 3 (moderate disability; requiring some help, but able to walk without assistance) 4 (moderately severe disability, unable to walk and attend to bodily needs without assistance), 5 (severe disability; bedridden, incontinent and requiring constant nursing care and attention) and 6 (dead) were defined as unfavourable outcome [25,27].

Psychological distress. Psychological distress was defined as clinically relevant symptoms of anxiety, depression and/or PTSD. Symptoms of depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS) [28], a self-report instrument specifically developed for hospitalized patients with medical conditions. Good reliability and validity with a Cronbach's alpha of 0.83 and 0.82 for the subscales anxiety and depression, respectively, has been demonstrated, as well as an optimal balance between sensitivity and specificity of approximately 0.80 when applying a cut-off score of $\geq$8 on both subscales [29]. Therefore, a score of $\geq$8 on the depression and/or anxiety subscale (range 0 to 21) of the HADS was considered as clinically relevant for the purpose of the study [28,29]. The HADS consists of 14 items and Cronbach's alpha for this population was $\alpha = .84$. PTSD symptoms were assessed by the Impact of Event Scale-Revised (IES-R) [30]. This self-report measure with 22 items covers three symptom domains, i.e., intrusion, avoidance, and hyperarousal. It shows high internal consistency with a Cronbach's alpha of 0.96 and good diagnostic accuracy at a cut-off score of 1.5 [31], which we applied in this study. Cronbach's alpha for this population was $\alpha = .92$.

Statistical analysis

Descriptive statistics, i.e., frequencies and percentages for binary and categorical variables, as well as medians and interquartile ranges for continuous variables were used to present socio-demographic and clinical characteristics of the study population. The primary endpoint was PICS defined as a physical, cognitive and/or psychological impairment measured with different scales as defined above (i.e., in one of the five outcome measures). To evaluate associations between potential risk factors and PICS at 3- and 12-month follow-up, logistic regression analyses were performed for the primary endpoint and separately for the three domains of PICS. As a measure of association, we report odds ratios (OR) and 95% confidence intervals (CI). In addition, univariable logistic regression analyses were adjusted for age and gender. We did not perform further multivariable analyses due to the low number of events to avoid overfitting. Further, a chi-square test and cross-tables were used to determine the persistence of patients with PICS between 3- and 12-month follow-up. Pearson correlations were calculated between the PICS domains physical, cognitive and psychological symptoms in a correlation matrix at 3 and 12 months. Stata 15 (StataCorp, College Station, Texas, USA) was used for all statistical analyses. Statistical significance was defined as a p-value of <0.05 (two-tailed).

Results

Study sample and baseline characteristics

One-hundred fifty-six patients completed at least one of two follow-up interviews; 139 (89.1%) patients completed the 3-month interview, and 110 (70.5%) the 12-month interview. Ninety-three (59.6%) participants completed both interviews. Eleven (7.1%) patients died between the 3- and 12-month follow-up. A flow diagram of the study population is shown in Fig 1.

Sociodemographic and clinical characteristics of the study population and for patients included in the 3-month and 12-month follow-ups are shown in Table 1. Median age of patients was 62.8 years and 17% were female. The median duration of ICU stay was 4 days and median hospital length of stay was 13 days. Patients had a high burden of comorbidities and cardiovascular risk factors.

Primary endpoint: PICS 3 months after hospitalization

Of 139 patients, 69 patients (49.6%) showed evidence of PICS 3 months after OHCA. Of those, 36.7% showed physical impairment, 25.2% cognitive impairment, and 12.9% psychological distress. Fig 1 shows the distribution of impairments among the different domains.

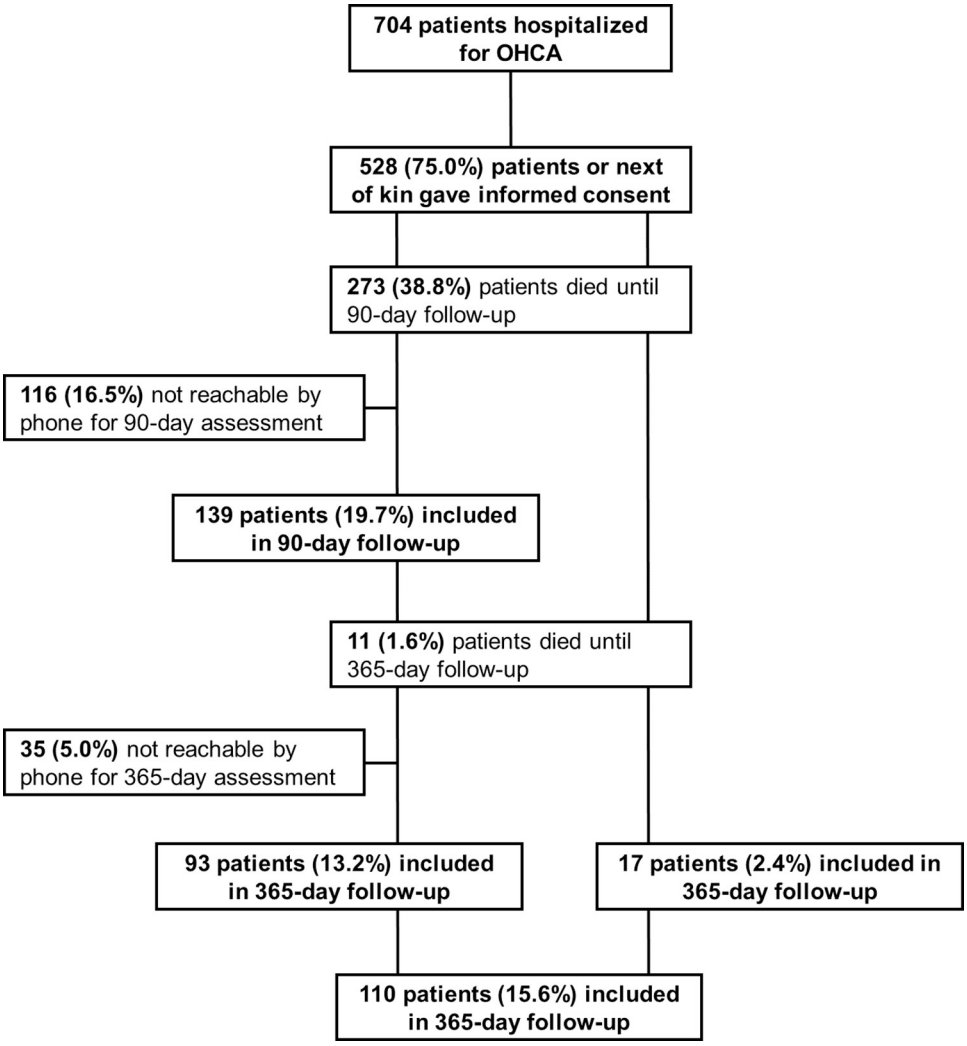

Fig 1. Flow diagram of the study population.

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Table 1. Sociodemographic and clinical characteristics of the study population.

Factor		All patients	3 months	12 months
N		156	139	110
Sociodemographics				
Age, median (IQR)		62.8 (54, 73.2)	63.2 (54.3, 73.5)	62.6 (53.9, 73.2)
Female, n (%)		27 (17.3%)	22 (15.8%)	17 (15.5%)
In partnership, n (%)		123 (80.9%)	109 (80.7%)	90 (82.6%)
Children, n (%)		128 (82.1%)	114 (82.0%)	92 (83.6%)
Highest education	School, n (%)	14 (11.0%)	12 (10.8%)	12 (11.9%)
	Diploma/ apprenticeship, n (%)	90 (70.9%)	79 (71.2%)	72 (71.3%)
	University, n (%)	23 (18.1%)	20 (18.0%)	17 (16.8%)
Employed at baseline, n (%)		72 (48.3%)	61 (46.2%)	54 (50.0%)
Setting of cardiac arrest				
Setting of cardiac arrest	At home	43 (28.7%)	38 (28.6%)	31 (29.0%)
	In public	95 (63.3%)	84 (63.2%)	69 (64.5%)
	IHCA	12 (8.0%)	11 (8.3%)	7 (6.5%)
Observed cardiac arrest		143 (91.7%)	126 (90.6%)	106 (96.4%)
	Bystander CPR	124 (79.5%)	112 (80.6%)	83 (75.5%)
	Professional bystander	39 (48%)	37 (47%)	26 (57%)
Initial rhythm	Ventricular tachycardia	8 (5.2%)	5 (3.6%)	7 (6.4%)
	Ventricular fibrillation	114 (73.5%)	102 (73.9%)	81 (74.3%)
	Asystole	7 (4.5%)	6 (4.3%)	6 (5.5%)
	Pulseless electrical activity	9 (5.8%)	9 (6.5%)	7 (6.4%)
	Unknown	17 (11.0%)	16 (11.6%)	8 (7.3%)
No-flow (min), median (IQR)		0 (0, 2)	0 (0, 2)	0 (0, 2)
Low-flow (min), median (IQR)		11 (8, 20)	12 (9, 20)	11.5 (8, 20)
Time until ROSC (min), median (IQR)		15 (10, 23)	15 (10, 25)	15 (10, 25)
Adrenaline	No adrenaline	77 (55.0%)	70 (56.0%)	56 (57%)
	>0 and <3 mg	33 (23.6%)	26 (20.8%)	23 (23%)
	≥3 mg	30 (21.4%)	29 (23.2%)	19 (19%)
Clinical scores at ICU arrival				
APACHE II, median (IQR)		25 (19, 30)	25 (20, 30)	25 (19, 30)
SAPS II, median (IQR)		58 (45, 66)	58 (43, 66)	58 (45, 68)
GCS, median (IQR)		4 (3, 14)	4 (3, 14)	5 (3, 14)
Days in ICU, median (IQR)		4 (2, 7)	4 (2, 7)	4 (2, 7)
Total days of hospital stay, median (IQR)		13 (8, 18)	13 (8, 17)	13 (8, 19)

Note: Data are presented as n (%) or median (interquartile range). Abbreviations: APACHE II, Acute Physiology And Chronic Health Evaluation Score II; SAPS II, Simplified Acute Physiology Score II; GCS, Glasgow Coma Scale; OHCA, out-o-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; IQR, interquartile range; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; IABP, intra-aortal balloon pump; mRS, modified Rankin Scale; CPC, Cerebral Performance Category.

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We assessed the association of several potential predictors with the risk for PICS at 3 months adjusted for age and gender (Table 2). Several factors were associated with PICS including baseline severity of illness scores (APACHE II: OR 1.07, 95%CI 1.02 to 1.12, p = 0.007 and SAPS II: OR 1.03, 95%CI 1.01 to 1.06, p = 0.006), intubation (OR 2.21, 95%CI 1.02 to 4.78, p = 0.043) and duration of intubation (in days) (OR 1.21, 95%CI 1 to 1.46, p = 0.046), length of ICU stay (in days) (OR 1.11, 95%CI 1.01 to 1.21, p = 0.022), functionality at discharge (poor mRS score: OR 4.35, 95%CI 1.7 to 11.1, p = 0.002 and CPC score: OR 3.39,

Table 2. Associations of predictor variables and post-intensive care syndrome at 3 months.

Factor		No PICS	PICS	OR (95%CI)	*p*	OR adjusted for age and gender (95%CI)	*p*
N		70	69				
Sociodemographics							
Age, median (IQR)		65.4 (58.6, 73.5)	61.1 (53.3, 73.3)	0.99 (0.97, 1.01)	0.46	*NA*	*NA*
Female, n (%)		9 (13%)	13 (19%)	1.57 (0.62, 3.96)	0.34	*NA*	*NA*
In partnership, n (%)		54 (79%)	55 (82%)	1.19 (0.5, 2.8)	0.69	1.25 (0.53, 2.99)	0.61
Children, n (%)		55 (79%)	59 (86%)	1.61 (0.67, 3.88)	0.29	1.73 (0.7, 4.28)	0.24
Highest education	School, n (%)	7 (12%)	5 (9%)	0.73 (0.22, 2.45)	0.61	0.95 (0.45, 2.02)	0.89
	Diploma/Apprenticeship, n (%)	38 (67%)	41 (76%)	1.58 (0.69, 3.62)	0.28	1.61 (0.7, 3.72)	0.27
	University, n (%)	12 (21%)	8 (15%)	0.65 (0.24, 1.75)	0.40	0.68 (0.25, 1.85)	0.45
Employed at baseline, n (%)		27 (41%)	34 (52%)	1.53 (0.77, 3.05)	0.22	1.69 (0.65, 4.36)	0.28
Setting of cardiac arrest							
Setting of cardiac arrest	At home	20 (29%)	18 (28%)	1.20 (0.66, 2.18)	0.55	1.27 (0.69, 2.35)	0.43
	In public	45 (65%)	39 (61%)				
	IHCA	4 (6%)	7 (11%)				
Observed cardiac arrest		63 (90%)	63 (91%)	1.16 (0.37, 3.67)	0.79	1.15 (0.37, 3.66)	0.80
	Bystander CPR	57 (81%)	55 (80%)	0.90 (0.39, 2.08)	0.80	0.89 (0.38, 2.09)	0.80
	Professional bystander	23 (55%)	14 (38%)	0.50 (0.20, 1.24)	0.13	0.48 (0.18, 1.31)	0.15
Initial rhythm	Ventricular tachycardia	4 (6%)	1 (1%)	1.05 (0.77, 1.44)	0.75	1.04 (0.77, 1.43)	0.77
	Ventricular fibrillation	52 (74%)	50 (74%)				
	Asystole	0 (0%)	6 (9%)				
	Pulseless electrical activity	6 (9%)	3 (4%)				
	Unknown	8 (11%)	8 (12%)				
No-flow (min), median (IQR)		0 (0, 4)	0 (0, 2)	1.01 (0.91, 1.12)	0.89	1.01 (0.91, 1.12)	0.91
Low-flow (min), median (IQR)		12 (10, 20)	12 (7, 23)	1.01 (0.99, 1.04)	0.36	1.01 (0.99, 1.04)	0.39
Time until ROSC (min), median (IQR)		15 (10, 21)	14 (8, 30)	1.01 (0.99, 1.04)	0.28	1.01 (0.99, 1.04)	0.32
Adrenaline	No adrenaline	38 (58%)	32 (53%)	1.19 (0.78, 1.82)	0.42	1.16 (0.75, 1.80)	0.50
	>0 and <3 mg	14 (22%)	12 (20%)				
	≥3 mg	13 (20%)	16 (27%)				
Clinical scores at ICU arrival							
APACHE II, median (IQR)		24 (17, 29)	26 (21, 31)	1.06 (1.02, 1.11)	**0.01**	1.07 (1.02, 1.12)	**0.007**
SAPS II, median (IQR)		55 (36, 65)	61 (51, 68)	1.03 (1.01, 1.05)	**0.01**	1.03 (1.01, 1.06)	**0.006**
GCS, median (IQR)		4 (3, 15)	4 (3, 8)	0.95 (0.89, 1.02)	0.17	0.96 (0.89, 1.02)	0.19

(*Continued*)

Table 2. (Continued)

Factor		No PICS	PICS	OR (95%CI)	*p*	OR adjusted for age and gender (95%CI)	*p*
Reason for OHCA							
Coronary heart disease, n(%)		45 (66%)	47 (69%)	1.14 (0.56, 2.35)	0.71	1.24 (0.59, 2.6)	0.57
Rhythmogenic, n(%)		13 (19%)	9 (13%)	0.65 (0.26, 1.63)	0.35	0.62 (0.24, 1.58)	0.32
Other or unclear reason, n (%)		10 (15%)	12 (18%)	1.24 (0.5, 3.11)	0.64	1.15 (0.45, 2.92)	0.77
Intensive care treatment							
Intubation, n (%)		44 (63%)	55 (80%)	2.32 (1.08, 4.97)	**0.03**	2.21 (1.02, 4.78)	**0.04**
Total days of intubation, median (IQR)		2 (1, 2)	2 (2, 6)	1.21 (1.01, 1.45)	**0.04**	1.21 (1, 1.46)	**0.046**
Targeted temperature management (TTM), n (%)		34 (49%)	43 (62%)	1.75 (0.89, 3.44)	0.10	1.74 (0.86, 3.5)	0.12
Vasoactives, n (%)		56 (80%)	51 (74%)	0.71 (0.32, 1.57)	0.40	0.68 (0.31, 1.52)	0.35
Impella / IABP, n (%)		4 (6%)	5 (7%)	1.29 (0.33, 5.02)	0.71	1.21 (0.3, 4.84)	0.79
Sedatives, n (%)		58 (83%)	65 (94%)	3.36 (1.03, 11)	**0.05**	3.18 (0.97, 10.48)	0.06
Coronary angiography, n (%)		61 (87%)	63 (91%)	1.55 (0.52, 4.61)	0.43	1.59 (0.53, 4.79)	0.41
Medical complications during ICU stay							
Aspiration, n (%)		29 (41%)	28 (41%)	0.97 (0.49, 1.9)	0.92	0.99 (0.5, 1.96)	0.98
Pneumonia, n (%)		31 (44%)	33 (48%)	1.15 (0.59, 2.25)	0.68	1.19 (0.61, 2.35)	0.61
Hemorrhage, n (%)		5 (7%)	7 (10%)	1.47 (0.44, 4.87)	0.53	1.52 (0.46, 5.1)	0.50
Delirium, n (%)		25 (36%)	22 (32%)	0.84 (0.42, 1.7)	0.63	0.87 (0.43, 1.78)	0.71
Renal failure, n (%)		7 (10%)	11 (16%)	1.71 (0.62, 4.7)	0.30	1.7 (0.61, 4.74)	0.31
Seizure, n (%)		2 (3%)	7 (10%)	3.84 (0.77, 19.18)	0.10	4.13 (0.82, 20.84)	0.09
Days in ICU, median (IQR)		4 (2, 5)	4 (2, 7)	1.1 (1.02, 1.2)	**0.02**	1.11 (1.01, 1.21)	**0.02**
Total days of hospital stay, median (IQR)		12 (7, 16)	14 (9, 18)	1.03 (0.99, 1.07)	0.14	1.03 (0.99, 1.08)	0.13
Poor mRS score at ICU discharge, n (%)		7 (10%)	22 (33%)	4.33 (1.7, 11.01)	**0.002**	4.35 (1.7, 11.1)	**0.002**
Poor CPC score at ICU discharge, n (%)		10 (14%)	24 (36%)	3.29 (1.43, 7.6)	**0.01**	3.39 (1.46, 7.88)	**0.005**
Follow-up on patients after 3 months							
Rehabilitation	None, n (%)	24 (34%)	19 (28%)	0.73 (0.35, 1.5)	0.39	0.72 (0.35, 1.5)	0.38
	Up to 3 weeks, n (%)	25 (36%)	25 (36%)	1.02 (0.51, 2.04)	0.95	1.04 (0.52, 2.09)	0.91
	More than 3 weeks, n (%)	21 (30%)	25 (36%)	1.33 (0.65, 2.69)	0.44	1.31 (0.64, 2.67)	0.46
Working status	Still working, n (%)	26 (42%)	22 (36%)	0.78 (0.38, 1.61)	0.51	0.49 (0.18, 1.35)	0.17
	Work lost, n (%)	1 (2%)	11 (18%)	13.42 (1.67, 107.53)	**0.01**	14.53 (1.8, 117.56)	**0.01**

(*Continued*)

Table 2. (Continued)

Factor		No PICS	PICS	OR (95%CI)	*p*	OR adjusted for age and gender (95%CI)	*p*
	No work prior to OHCA, n (%)	35 (56%)	28 (46%)	0.65 (0.32, 1.33)	0.24	0.51 (0.18, 1.46)	0.21

Note: Data are presented as n (%) or median (interquartile range). Abbreviations: IQR, interquartile range; ROSC, return to spontaneous circulation; IABP, intra-aortal balloon pump; mRS, modified Rankin Scale; CPC, Cerebral Performance Category; APACHE II, Acute Physiology And Chronic Health Evaluation Score II; SAPS II, Simplified Acute Physiology Score II.

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95%CI 1.46 to 7.88, p = 0.005), as well as work loss within the observed 3 months (OR 14.53, 95%CI 1.8 to 117.56, p = 0.012).

Secondary endpoint: PICS 12 months after hospitalization

Of 110 patients, 52 patients (47.3%) showed evidence of PICS after 12 months with 36.7% showing physical impairment, 22.2% cognitive impairment, and 12.7% psychological distress (Fig 2). We assessed potential predictors for PICS (Table 3) and found initial severity of illness scores (APACHE II: OR 1.08, 95%CI 1.02 to 1.14, p = 0.008) and functionality at discharge (poor mRS score: OR 3.97, 95%CI 1.42 to 11.12, p = 0.009; and CPC score: OR 3.22, 95%CI 1.29 to 8.04, p = 0.012) to be associated with PICS. In addition, risk for PICS was lower in patients not needing rehabilitation (OR 0.31, 95%CI 0.12 to 0.82, p = 0.019) and in turn increased with longer duration of the rehabilitation (in days) (OR 1.24, 95%CI 1.03 to 1.5, p = 0.027).

We also investigated, in the 93 patients that were assessed at both time points, whether PICS at 3-month would persist after 12-month. Results stratified according to PICS at both time points are shown in Fig 3**.** Chi-square test between PICS at 3 and 12 months was significant, $X^2(1, N = 93) = 23.6$, $p < .001$. Further, we investigated how the different domains of PICS were inter-correlated by calculation of a correlation matrix at 3- and 12-month as shown

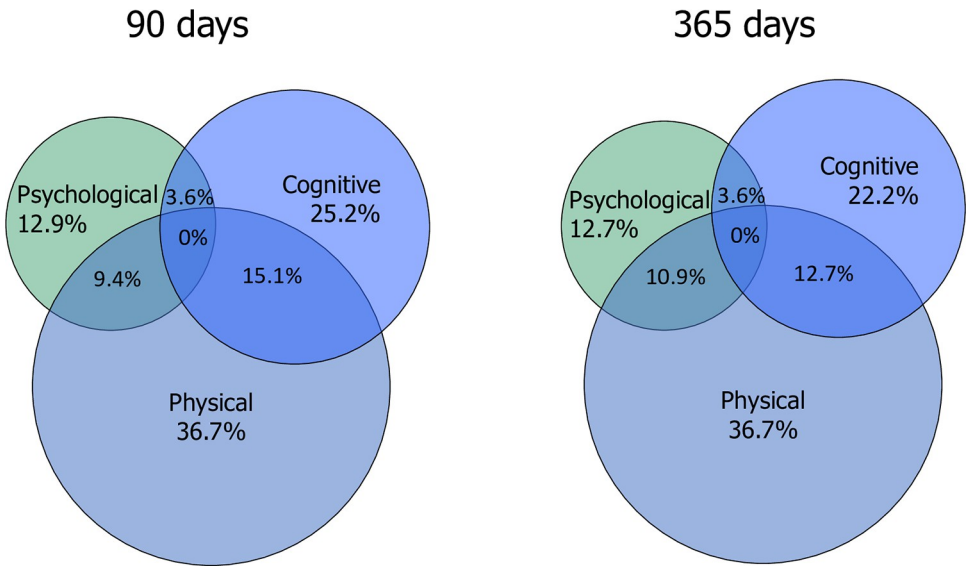

Fig 2. Co-occurrence of post-intensive care syndrome domains at 3 and 12 months. Note: Post-intensive care syndrome domains, i.e. physical, cognitive and psychological symptoms, and overlaps between the different domains.

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Table 3. Associations of predictor variables and post-intensive care syndrome at 12 months.

Factor		No PICS	PICS	OR (95% CI)	*p*	OR adjusted for age and gender (95% CI)	*p*
N		58	52				
Sociodemographics							
Age, median (IQR)		63.4 (54, 72.4)	61.1 (53.4, 74.5)	1.01 (0.98, 1.04)	0.49	*NA*	*NA*
Female, n (%)		8 (14%)	9 (17%)	1.31 (0.46, 3.69)	0.61	*NA*	*NA*
In partnership, n (%)		48 (84%)	42 (81%)	0.79 (0.29, 2.12)	0.64	0.78 (0.29, 2.11)	0.62
Children, n (%)		46 (79%)	46 (88%)	2 (0.69, 5.78)	0.20	1.85 (0.62, 5.5)	0.27
Highest education	School, n (%)	6 (12%)	6 (12%)	1.07 (0.32, 3.57)	0.91	1.17 (0.31, 4.34)	0.82
	Diploma/apprenticeship, n (%)	34 (65%)	38 (78%)	1.83 (0.76, 4.42)	0.18	1.79 (0.73, 4.36)	0.2
	University, n (%)	12 (23%)	5 (10%)	0.38 (0.12, 1.17)	0.09	0.37 (0.12, 1.15)	0.09
Employed at baseline, n (%)		29 (51%)	25 (49%)	0.93 (0.44, 1.98)	0.85	1.19 (0.45, 3.1)	0.73
Setting of cardiac arrest							
Setting of cardiac arrest	At home	14 (25%)	17 (33%)	0.83 (0.41, 1.64)	0.58	0.82 (0.41, 1.66)	0.59
	In public	39 (70%)	30 (59%)				
	IHCA	3 (5%)	4 (8%)				
Observed cardiac arrest		54 (93%)	52 (100%)	1	-	1	-
	Bystander CPR	46 (79%)	37 (71%)	0.64 (0.27, 1.54)	0.32	0.59 (0.24, 1.45)	0.25
	Professional bystander	15 (54%)	11 (61%)	1.36 (0.41, 4.54)	0.62	1.71 (0.42, 6.90)	0.45
Initial rhythm	Ventricular tachycardia	5 (9%)	2 (4%)	0.77 (0.51, 1.16)	0.21	0.77 (0.51, 1.17)	0.22
	Ventricular fibrillation	41 (71%)	40 (78%)				
	Asystole	1 (2%)	5 (10%)				
	Pulseless electrical activity	3 (5%)	4 (8%)				
	Unknown	8 (14%)	0 (0%)				
No-flow (min), median (IQR)		0 (0, 2)	0 (0, 2)	1.07 (0.96, 1.20)	0.24	1.08 (0.96, 1.21)	0.20
Low-flow (min), median (IQR)		11 (9, 17)	12 (6, 30)	1.02 (0.99, 1.05)	0.21	1.02 (0.99, 1.06)	0.13
Time until ROSC (min), median (IQR)		15 (10, 20)	20 (8, 30)	1.02 (0.99, 1.05)	0.13	1.03 (1, 1.06)	0.07
Adrenaline	No adrenaline	36 (69%)	20 (43%)	2.03 (1.19, 3.47)	**0.01**	2.30 (1.30, 4.09)	**0.004**
	>0 and <3 mg	10 (19%)	13 (28%)				
	≥3 mg	6 (12%)	13 (28%)				
Clinical scores at ICU arrival							
APACHE II, median (IQR)		24 (17, 28)	28 (22, 32)	1.08 (1.02, 1.14)	**0.01**	1.08 (1.02, 1.14)	**0.01**
SAPS II, median (IQR)		58 (39, 66)	60 (50, 70)	1.02 (1, 1.05)	0.11	1.02 (0.99, 1.05)	0.13
GCS, median (IQR)		5 (3, 15)	4 (3, 9)	0.97 (0.90, 1.04)	0.38	0.96 (0.89, 1.04)	0.30
Reason for OHCA at ICU admission							

(*Continued*)

Table 3. (Continued)

Factor		No PICS	PICS	OR (95% CI)	*p*	OR adjusted for age and gender (95% CI)	*p*
Coronary heart disease, n (%)		38 (70%)	33 (63%)	0.73 (0.32, 1.65)	0.45	0.75 (0.32, 1.73)	0.49
Rhythmogenic, n (%)		10 (19%)	11 (21%)	1.18 (0.45, 3.07)	0.73	1.17 (0.44, 3.12)	0.75
Other or unclear reason, n (%)		6 (11%)	8 (15%)	1.45 (0.47, 4.52)	0.52	1.39 (0.44, 4.39)	0.58
Intensive care treatment							
Intubation, n (%)		37 (64%)	41 (79%)	2.12 (0.9, 4.97)	0.09	2.34 (0.97, 5.64)	0.06
Total days of intubation, median (IQR)		2 (1, 2)	2 (1, 6)	1.21 (0.98, 1.49)	0.08	1.25 (0.99, 1.58)	0.07
Targeted temperature management (TTM), n (%)		30 (52%)	31 (60%)	1.38 (0.65, 2.94)	0.41	1.61 (0.71, 3.63)	0.25
Vasoactives, n (%)		47 (81%)	38 (73%)	0.64 (0.26, 1.56)	0.32	0.65 (0.26, 1.59)	0.34
Impella / IABP, n (%)		5 (9%)	7 (13%)	1.65 (0.49, 5.55)	0.42	1.89 (0.54, 6.59)	0.32
Sedatives, n (%)		49 (84%)	48 (92%)	2.2 (0.64, 7.64)	0.21	2.28 (0.65, 8.02)	0.20
Coronary angiography, n (%)		50 (86%)	45 (87%)	1.03 (0.35, 3.06)	0.96	1.14 (0.37, 3.51)	0.82
Medical complications during ICU stay							
Aspiration, n (%)		25 (43%)	20 (38%)	0.83 (0.38, 1.77)	0.62	0.87 (0.4, 1.9)	0.73
Pneumonia, n (%)		28 (48%)	25 (48%)	0.99 (0.47, 2.1)	0.98	1.05 (0.49, 2.25)	0.90
Hemorrhage, n (%)		3 (5%)	8 (15%)	3.33 (0.83, 13.31)	0.09	3.36 (0.83, 13.54)	0.09
Delirium, n (%)		18 (31%)	18 (35%)	1.18 (0.53, 2.61)	0.69	1.18 (0.53, 2.64)	0.68
Renal failure, n (%)		5 (9%)	10 (19%)	2.52 (0.8, 7.95)	0.11	2.46 (0.77, 7.81)	0.13
Seizure, n (%)		2 (3%)	4 (8%)	2.33 (0.41, 13.3)	0.34	2.63 (0.45, 15.27)	0.28
Days in ICU, median (IQR)		4 (2, 8)	4.5 (2, 7)	1.03 (0.96, 1.11)	0.39	1.05 (0.97, 1.13)	0.27
Total days of hospital stay, median (IQR)		13 (8, 16)	14 (7, 21)	1.03 (0.98, 1.07)	0.22	1.03 (0.98, 1.07)	0.20
Poor mRS score at ICU discharge, n (%)		6 (11%)	17 (33%)	4.05 (1.45, 11.29)	**0.01**	3.97 (1.42, 11.12)	**0.01**
Poor CPC score at ICU discharge, n (%)		9 (16%)	20 (38%)	3.26 (1.32, 8.08)	**0.01**	3.22 (1.29, 8.04)	**0.01**
Follow-up on patients after 3 months							
Rehabilitation	None	19 (33%)	7 (13%)	0.32 (0.12, 0.84)	**0.02**	0.31 (0.12, 0.82)	**0.02**
	Up to 3 weeks	21 (36%)	16 (31%)	0.78 (0.35, 1.74)	0.55	0.79 (0.36, 1.77)	0.57
	More than 3 weeks	18 (31%)	29 (56%)	2.8 (1.28, 6.11)	**0.01**	2.88 (1.3, 6.38)	**0.01**
Working status	Still working	26 (48%)	17 (36%)	0.61 (0.27, 1.36)	0.23	0.69 (0.23, 2.01)	0.49

(*Continued*)

Table 3. (Continued)

Factor		No PICS	PICS	OR (95% CI)	*p*	OR adjusted for age and gender (95% CI)	*p*
	Work lost	3 (6%)	7 (15%)	2.98 (0.72, 12.24)	0.13	3.07 (0.74, 12.82)	0.12
	No work prior to OHCA	25 (46%)	23 (49%)	1.11 (0.51, 2.43)	0.79	0.72 (0.24, 2.11)	0.55

Note: Data are presented as n (%) or median (interquartile range). Abbreviations: IQR, interquartile range; ROSC, return to spontaneous circulation; IABP, intra-aortal balloon pump; mRS, modified Rankin Scale; CPC, Cerebral Performance Category; APACHE II, Acute Physiology And Chronic Health Evaluation Score II; SAPS II, Simplified Acute Physiology Score II.

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in Table 4. Correlations between PICS domains at 3-month follow-up showed significant correlations between the physical and psychological domain and between the physical and cognitive domain. Similar results were found at 12-month follow-up.

Discussion

In this prospective observational cohort study, we found that nearly half of our OHCA survivors suffered from long-term health impairments after their ICU stay. One in three patients showed physical impairments, one in four had cognitive impairments, and one in eight patients psychological distress. These findings were comparable at 3 and 12 months following cardiac arrest with similar percentages overall and within domains. We found weak, yet significant correlations between domains except for the psychological and cognitive domain. Furthermore, several baseline predictors were identified as potential risk factors.

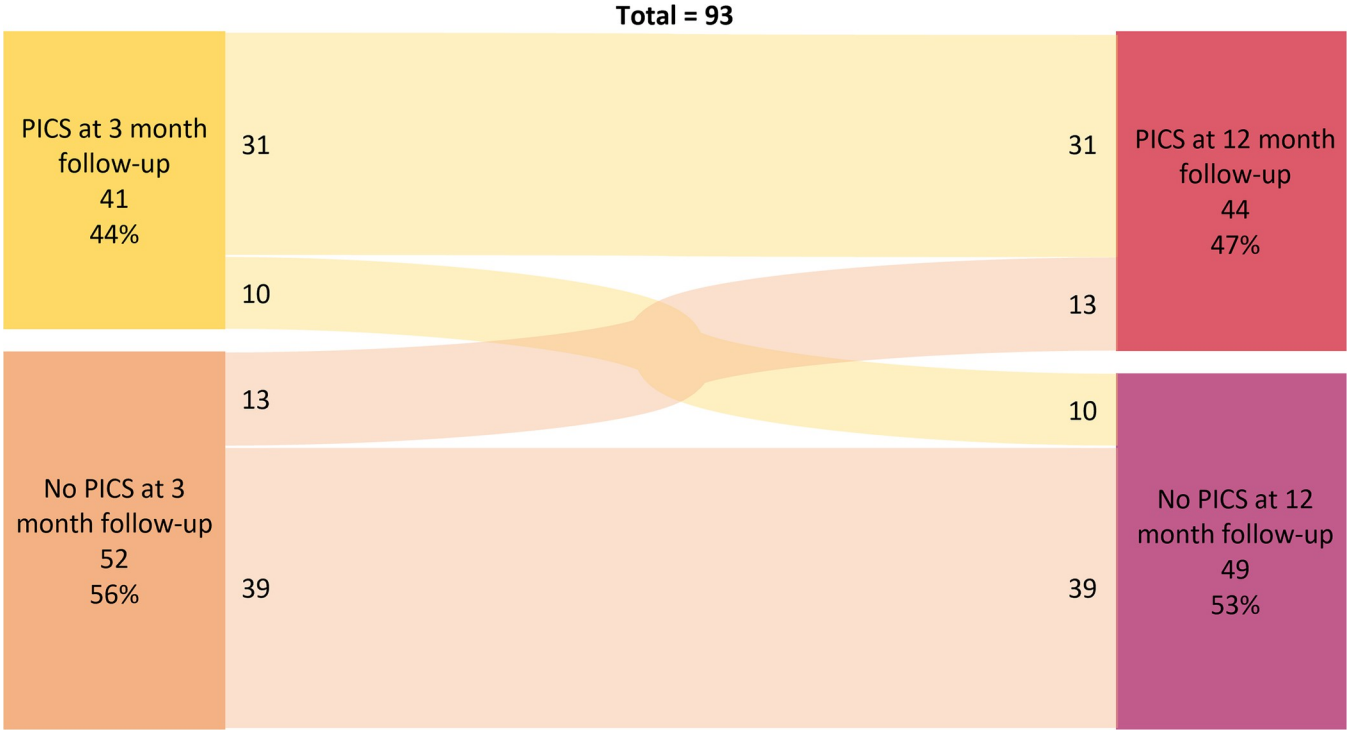

Fig 3. Sankey diagram of occurrence of PICS or no PICS at 3 and 12 months.

https://doi.org/10.1371/journal.pone.0276011.g003

Table 4. Correlation matrix of physical, cognitive and psychological domain at 3- and 12-month follow-up.

PICS domains at 3 months				PICS domains at 12 months		
	Physical domain	Cognitive domain	Psychological domain	Physical domain	Cognitive domain	Psychological domain
Physical domain	-	-	.	-	-	-
Cognitive domain	0.28, p<0.001	-	-	0.25, p<0.01	-	-
Psychological domain	0.28, p<0.001	0.02, p = 0.79	-	0.39, p<0.001	0.06, p = 0.55	-

Note: Data reported in Pearson correlation coefficient r.

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This study has several important implications. First, the prevalence of PICS found in our cohort of OHCA surviors is comparable to other cohorts of general ICU patients at 3 and 12 months [8]. Yet, there are differences in the distribution among PICS domains. We found similar rates of physical impairments of almost 40% in our cohort compared to studies from the general ICU patient population [32]. In contrast to other reports showing an improvement in self-assessed health at long-term [11,12], our cohort was fairly stable within the 12 months of investigation. Furthermore, we found cognitive impairments in 25% and 22% of patients at 3 and 12 months. Importantly, these numbers may be influenced by the instrument used for assessment: objective assessments of cognitive impairment have found higher prevalences compared to subjective assessments [13]. We used a subjective instrument for assessing cognitive impairment [33], which may explain the lower risks, which is again in line with other reports [14]. Also, one third to nearly half of ICU patients have been found to suffer from mental health issues [34,35]. For OHCA patients, previous reports ranged between 14% to 45% for depression and from 13% to 61% for anxiety, again dependent on the instrument and cut-offs used [15]. Our findings of 13% at both time points are thus in the lower range of these studies [15].

Second, several clinical and psychosocial factors were related to developing PICS at 3 months including severity of illness, adrenaline, intubation, functionality at discharge and work loss within 3 months post-discharge. These risk factors, however, are challenging to modify. Prolonged mechanical ventilation or deep sedation have previously been found to aggravate symptoms of PICS [36,37]. Thus, daily stop of anesthetics to avoid oversedation, early weaning strategies and use of lower sedative drug doses have become an important goal in any ICU patient care [37,38]. Additionally, we found that the need for rehabilitation and prolonged rehabilitation were associated with PICS 12 months after OHCA. Our data indicate that during rehabilitation, screening for PICS could help identify high-risk patients needing medical and psychological support, which in turn may reduce their risk in the long term. This may be important not only for the individual patient but also on a larger economic and social level [39].

Similarly, cognitive impairment at discharge assessed by the mRS and CPC score was associated with PICS 3 and 12 months following OHCA. This association may at least partially be explained by the cognitive impairments we had already found at baseline persisting in the long-term. This is in line with research, showing that most recovery of cognitive function in ICU patients occurred within the first 3 months with only little improvements after 12 months [40]. Thus, measures of cognitive functioning may be useful in screening patients to predict long-term PICS early on.

Interestingly, no patients had impairments in all three PICS domains at neither time point of assessment. This is in line with other results in general ICU patients: Marra et al. found a 56% prevalence of PICS-related complaints when considering one or more domains, but a much lower prevalence when complaints in all three domains were considered (i.e., 4% after

12 months) [8]. Concerning the co-occurrence of the different PICS domains, we found weak, yet significant correlations between domains except between the psychological and cognitive domains. This coincides with findings in OHCA patients that show health-related quality of life to be associated with cognitive impairments [14,41], as well as with psychological distress [14,16], yet finding mixed results in associations between psychological distress and cognitive impairment [16,42]. Possibly, PICS in OHCA patients falls into two subgroups: physically and cognitively impaired patients, or physically impaired and psychologically distressed patients. However, this hypothesis must be validated in future research.

Our findings suggest that PICS at 3 months is highly predictive for PICS after 12 months. At the same time, our data show that 11 patients newly developed physical impairment, 6 developed cognitive impairment and 8 patients developed psychological distress at twelve-month follow-up. Research shows levels of psychological distress and self-assessed health to improve among OHCA survivors in the long term [11,12], yet only minor improvements have been found in cognitive performance from 3 to 12 months [14]. However, these results are average findings and are comparable to our percentual stability of PICS impairments over time. Yet to the best of our knowledge, no analysis has assessed the course of symptoms as fine-grained as our study, therefore, intraindividual trajectories in other studies remain unclear. Possibly, due to patients' self-report as only information, subjective health impairment may become more visible in everyday life over time.

This trial is strengthened by the prospective and consecutive inclusion of study patients. Yet, it also has several limitations. As an observational study, the results are in need for interventional research to prove causality. Also, due to the sample size the power of the study is limited. Further, 83% of the study cohort are men, however, we adjusted for gender in the multivariable model to control for possible confounding. Also, patient outcomes were assessed subjectively, therefore outcomes might differ to objective outcome measures. Further, as several patients were not reachable at either 3- or 12-month follow-up, only a subgroup could be assessed for PICS trajectories over time. Also, as a single-center study, there is a lack of generalizability to other institutions and countries. Therefore, multicenter and multinational studies are necessary to validate our findings. Further, since no single definition of PICS exists, comparability with other study findings is limited. We do not expect biased results by the telephone assessment, as no difference has been found between face-to-face and telephone self-report measures [43]. Within this hypothesis generating study, we aimed to understand the possible associations of baseline factors and long-term risk for PICS. Because there is insufficient literature on this topic, we did not preselect variables but present the full list of predictors and due to the limited number of events, we adjusted the analysis only for age and gender. The high number of tests makes type II error possible and prospective validation is needed in an independent cohort. Finally, in our analysis acute physiology parameters wane in importance as time from OHCA passes, but mRS and CPC continue to dominate the associations. This may be indeed specific to the population of OHCA patients with brain injury and may differ in other ICU populations. However, more data is needed to better understand the influence on brain injury on long-term risk for PICS.

Conclusions

With a growing number of patients surviving their ICU stay after an OHCA and nearly half of all OHCA survivors displaying evidence of PICS up to one year after ICU admission, appropriate screening and management is necessary to minimize the risk for PICS and to meet the increased need for its treatment. Future studies should evaluate whether early identification of these patients enables preventive strategies.

Supporting information

S1 Database.
(XLSX)

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Appendix D

Study IV

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Review

Medical futility regarding cardiopulmonary resuscitation in in-hospital cardiac arrests of adult patients: A systematic review and Meta-analysis

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Abstract

Aim: For some patients, survival with good neurologic function after cardiopulmonary resuscitation (CPR) is highly unlikely, thus CPR would be considered medically futile. Yet, in clinical practice, there are no well-established criteria, guidelines or measures to determine futility. We aimed to investigate how medical futility for CPR in adult patients is defined, measured, and associated with do-not-resuscitate (DNR) code status as well as to evaluate the predictive value of clinical risk scores through meta-analysis.

Methods: We searched Embase, PubMed, CINAHL, and PsycINFO from the inception of each database up to January 22, 2021. Data were pooled using a fixed-eects model. Data collection and reporting followed the PRISMA guidelines.

Results: Thirty-one studies were included in the systematic review and 11 in the meta-analysis. Medical futility defined by risk scores was associated with a significantly higher risk of in-hospital mortality (5 studies, 3102 participants with Pre-Arrest Morbidity (PAM) and Prognosis After Resuscitation (PAR) score; overall RR 3.38 [95% CI 1.92–5.97]) and poor neurologic outcome/in-hospital mortality (6 studies, 115,213 participants with Good Outcome Following Attempted Resuscitation (GO-FAR) and Prediction of Outcome for In-Hospital Cardiac Arrest (PIHCA) score; RR 6.93 [95% CI 6.43–7.47]). All showed high specificity (>90%) for identifying patients with poor outcome.

Conclusion: There is no international consensus and a lack of specific definitions of CPR futility in adult patients. Clinical risk scores might aid decision-making when CPR is assumed to be futile. Future studies are needed to assess their clinical value and reliability as a measure of futility regarding CPR.

Keywords: Medical futility, Cardiopulmonary resuscitation, Clinical risk score, Do not resuscitate, In-hospital mortality, Neurological outcome

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Introduction

Background

Patients requiring cardiopulmonary resuscitation (CPR) for an in-hospital cardiac arrest (IHCA) have a high risk of mortality and only about 17% to 22% survive until hospital discharge.[1–4] Additionally, a considerable proportion of CPR survivors suffer from subsequent neurologic disabilities.[2,4,5] Despite advances in critical care and resuscitation measures, survival rates have only slightly increased during the last decades[5–7] and even decreased in some patient groups, such as elderly patients.[3] While CPR was originally intended for patients who experience a sudden and unexpected cardiac arrest with a presumed high chance of functional recovery,[8] the intervention has become a standard procedure performed in almost any cases of cardiac arrests.[9] However, in hospitalized patients with severe illness and/or debilitating comorbidities survival to discharge with a favorable neurologic outcome is highly unlikely. In such patients, CPR may be considered medically futile.[1,10] Yet, in clinical practice, there are no established criteria to determine medical futility regarding resuscitation in case of IHCA.

Importance

The concept of medical futility regarding resuscitation has been discussed for decades with no international consensus being achieved. Common criticisms concern the usefulness and implementation of futility in clinical practice due to a lack of established criteria and ethical considerations.[11,12] Still, futility remains an essential topic for clinical decision-making in daily practice.[1,13] There are national guidelines such as the medical-ethical guidelines on code status decisions published by the Swiss Academy of Medical Sciences.[14] These state that resuscitation is indicated if there is a chance that the patient survives without severe neurologic impairments. However, because definitions of futility are rather vague and lack specific criteria, implementation in clinical practice remains difficult. There have been different attempts to define futility based solely on expected in-hospital mortality rates without considering neurological outcome.[15] However, accurate estimation of survival after CPR is challenging and varies significantly among different physicians.[16] In one study, physicians have overestimated the likelihood of survival of adult patients with IHCA by as much as 300%,[17] while another study found that physicians can predict patient survival after IHCA no better than chance.[18] Further, a significant number of patients with a very low likelihood of survival after IHCA still have no do-not-resuscitate (DNR) orders in place in clinical practice.[19]

Goals of this investigation

The objective of this systematic review and meta-analysis was to understand the concept of medical futility regarding CPR in case of IHCA of adult patients by investigating definitions of medical futility regarding resuscitation, assessment of futility for in-hospital CPR, and the prevalence of DNR orders in hospitalized patients in whom CPR would be deemed futile.

Methods

Types of studies, participants, and outcomes

Data collection and reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.[20] We included peer-reviewed studies discussing and/or evaluating medical futility regarding CPR in adult hospitalized patients. Studies were eligible if they reported either a definition of futility regarding CPR, clinical measures to assess futility, and/or rates of DNR orders in patients for whom CPR attempt was deemed futile. No restrictions concerning age or gender of adult participants were applied. No publication date restrictions and no language restrictions were used.

Studies were excluded if one of the following criteria was present: 1) medical futility regarding resuscitation not addressed / population does not include patients in whom futility regarding resuscitation is assessed, 2) patients < 18 years, 3) no clinical peer-reviewed study or conference poster/abstract, and 4) no information on any of the predefined outcome parameters.

Due to the exploratory nature of our study, we did not define specific hypotheses. This manuscript is based on the MOOSE Checklist of Meta-analyses and Observational Studies (see eTable 2 in the Supplementary Material).[21]

Search terms for identification of studies

We searched the digital databases Embase, PubMed, CINAHL and PsycINFO, using a comprehensive search strategy consisting of a combination of subject headings and free-text words. The search strategy was developed together with a librarian (H.E.) experienced in systematic reviews. The final search strategy is provided in the Supplementary Material to ensure traceability and reproducibility of our results. To identify additional studies, we screened all references of eligible studies through the cited reference search of Web of Science and PubMed and applied the similar articles search of PubMed. The latest search was performed on January 22, 2021.

Study selection

Three investigators (H.C., A.V. and K.B.) screened the titles and abstracts of articles regarding inclusion and exclusion criteria. Two reviewers (H.C. and A.V.) independently assessed the full texts of all remaining studies and disagreements were resolved through discussion with a third reviewer (K.B.).

Risk of bias evaluation

We evaluated the risk of bias for every relevant outcome of all included studies using The Cochrane Collaboration's tool for assessing risk of bias.[22] Two authors (K.B. and A.V.) independently assessed the risk of bias for all studies and resolved disagreements by discussion until consensus was found. A detailed description of the risk of bias assessment can be found in the Supplementary Material.

Analysis

We express dichotomous data risk ratios (RR) with 95% confidence intervals (CI). Data were pooled using a fixed-effects model. Heterogeneity (inconsistency) was identified through visual inspection of the forest plots. We used the I^2 statistic, which quantifies inconsistency across studies, to assess the consequences of heterogeneity on the meta-analysis. A considerable level of heterogeneity is indicated by an I^2 statistic of 50% or more.[23] Cut-off values for stratification were chosen based on the frequently used cut-offs in the literature.[24–28] Accordingly, a PAM or PAR score > 8, a GO-FAR score $\geq$ 14 and a PIHCA score $\leq$ 3% indicate that CPR would be

medically futile. We also calculated the risk scores' specificity separately for each study. We applied narrative synthesis if data were not suitable for direct comparison.

Statistical analyses were performed using the METAN package in Stata (Stata MP, version 15.1; StataCorp LP), and a two-sided $p < .05$ was considered statistically significant.

Results

Identified studies

A total of 1966 records were identified through database searches and other sources. We removed duplicates (n = 86) and discarded 1621 studies after screening titles and abstracts. Of the remaining 259 full-text articles, 31 studies[1,4,24–52] were eligible for inclusion (Fig. 1).

Description of studies

Table 1 lists characteristics of the 11 studies included in the meta-analysis. Detailed information on the remaining 20 studies solely included in the qualitative synthesis are shown in eTable 2. Publication dates ranged from 1989 to 2019, and studies were conducted mostly in the United States,[24,26,27,29,34,35,39,42,45,47,48] and in European countries such as Sweden,[4,28,31,49] and England.[40,41,44] Study sample sizes ranged from 29 to 96,499 per trial. Half of the studies included hospitalized patients receiving CPR after IHCA[1,4,24,33,34,26–28,41–43,46–49] and in three studies the study population consisted of hospitalized patients without IHCA.[25,30,40,52] Yet, some studies included more specific patient populations such as elderly patients,[35,44] oncological patients,[36,38] critically ill patients,[39] severe burn patients,[32] or patients with multiple IHCA.[29] One study only included patients with established DNR orders.[45]

Definitions of futility

Twenty-seven studies included short descriptions or definitions of medical futility for CPR. These varied broadly in content and specificity, and rarely consisted of more than one or two sentences. Six studies defined futility as a very low likelihood of survival after CPR following cardiac arrest[1,10,33,39,45,52] with one of them specifying a "1% chance of surviving 2 months after CPR".[39] Nine studies evaluating clinical risk scores solely presented a cut-off score indicating futility[24,42,44,52] or extremely low chance of survival with favorable neurologic outcome, defined as Cerebral Performance Category 1[10,47,48] or 1 to 2.[28,49] Ten studies provided unspecific definitions, defining futility either based on clinical conditions, e.g., age, metastatic cancer, or "acute or chronic impairments in almost any organ system in elderly patients" or based on an outcome, e.g., "prolonging the patient's suffering and therefore harming the patient".[25,30,31,35,36,38,40,45,50,51] However, none of these definitions included specific thresholds or criteria for futility. Four studies reported specific scenarios in which CPR would be futile, such as patients with a recurrent cardiac arrest or severe burn injuries.[29,32,34,37]

DNR code status in patients for whom CPR was deemed futile

Four studies reported how many patients for whom CPR was deemed futile had a DNR code status.[39,40,44,52] The definitions of futility among these studies and the rates of DNR code status varied considerably. In the study of Aarons et al.[40] junior doctors gave a statement concerning the appropriateness of resuscitation in case of IHCA for each included patient. Of all patients for whom CPR was perceived as futile, 27% (n = 24) had DNR orders. Stewart et al.[44] evaluated medical inpatients with a mean age of 84 years. CPR was judged futile if the patients' Pre-Arrest Morbidity (PAM) index scores were >4 and their Prognosis After Resuscitation (PAR) scores were >5 at the same time. Of these patients where CPR was considered to be futile, 44% (n = 17) had a DNR code status. Becker et al.[52] assessed 2889 patients hospitalized at the Division of Traumatology/Orthopedics or Internal Medicine. Futility regarding CPR was defined as a Good Outcome Following Attempted Resuscitation (GO-FAR) score $\geq$ 14 and/or a Clinical Frailty Scale (CFS) rating of $\geq$7. Of all patients where CPR was determined futile (n = 467), 69.2% had a DNR code status documented in their medical charts. Teno et al.[39] calculated a time-to-event prediction model in a sample of critically ill patients including diagnosis, age, number of hospital days before study entry, cancer diagnosis, neurologic function, and several physiologic measures all assessed on day 3 after study entry. CPR was determined as futile if the chance of 2-month survival was estimated to be 1% or less. The majority of those patients, i.e., 71% (n = 82) had a DNR order.

Meta-analysis of pre-arrest risk scores

The included studies examined different pre-arrest factors and pre-arrest risk scores based on these factors. Several risk scores were found in the systematic search to assess the pre-arrest risk of death during hospitalization after CPR for IHCA in individual patients. Eleven studies were included in the meta-analysis[4,24,41,43,26–28,46–49] that assessed the following four pre-arrest risk scores: the Pre-arrest morbidity (PAM) index, the Prognosis After Resuscitation (PAR) score, the Good Outcome Following Attempted Resuscitation (GO-FAR) score and the Prediction of Outcome for In-Hospital Cardiac Arrest (PIHCA) score. In the supplementary material, we provide a detailed overview of these clinical risk scores (eTable 1).

In the studies included in the meta-analysis, the mean age varied between 60 years[48] and 72 years.[49] Further, male gender ranged between 58 %[27,47] and 65%.[24,48] All studies included inpatients receiving CPR after IHCA. Overall, the meta-analysis comprised 118,315 patients.

Five studies with 1621 patients reported PAM scores and in-hospital mortality with a low risk of bias.[24,26,41,43,46] The overall analysis showed that the PAM index was associated with a significantly higher risk of in-hospital death at a cut-off score of PAM > 8 (RR 4.10 [95 %CI 1.39–12.11]). Heterogeneity among trials was low (I^2 = 0.0%, p = .638). Specificity in the individual studies ranged from 98% to 100% (eTable 3).

Four studies with 1481 patients reported PAR scores and mortality with a low risk of bias.[26,41,43,46] The PAR score was associated with a significantly higher risk of death until discharge at a cut-off score of PAR > 8 (RR 3.11 [95 %CI 1.59–6.05]). Heterogeneity among trials did not have a significant impact (I^2 = 54.5%, p = .086). Results of the PAM and PAR scores are shown in Fig. 2. Specificity in the individual studies ranged from 83% to 100% (eTable 3).

Five studies with 114,585 patients reported GO-FAR scores and poor neurologic outcome or in-hospital death with a low risk of bias.[4,27,28,47,48] The GO-FAR score was associated with a significantly higher risk of poor neurologic outcome (CPC $\leq$ 1) and in-hospital death at a cut-off score of GO-FAR $\geq$ 14 (RR 6.92 [95 %

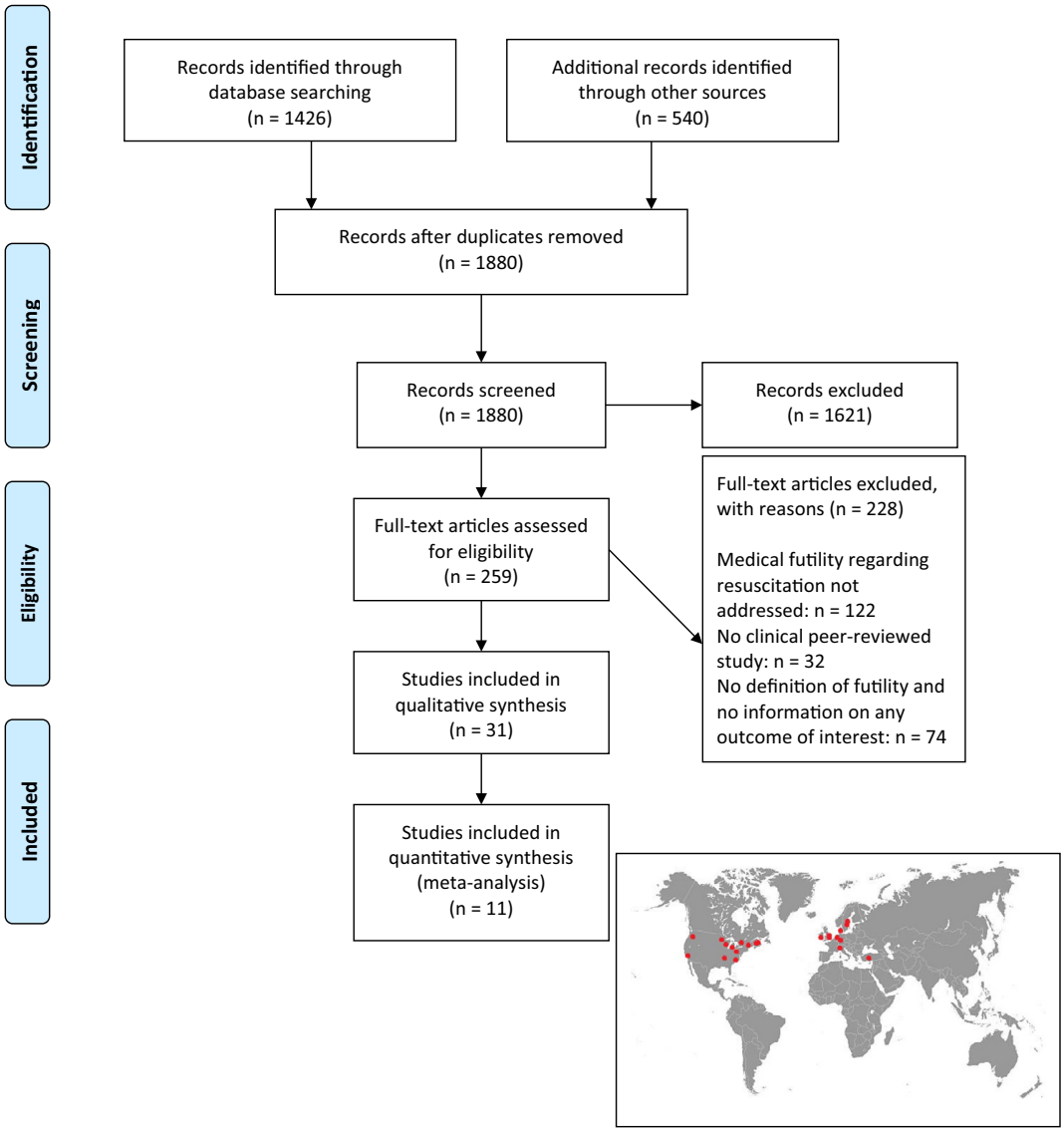

Fig. 1 – PRISMA flow diagram of the study selection process.

CI 6.42–7.46]). There was high heterogeneity among trials (I^2 = 81.1%, p < .001). Specificity in the individual studies ranged from 89% to 97% (eTable 3).

One study with 628 patients evaluated the PIHCA score[49] and poor neurologic outcome or in-hospital death with a low risk of bias. A very low or low (≤3% chance of favorable neurological survival) PIHCA score was associated with a significantly higher risk of poor neurologic outcome (CPC ≤ 2) and death until discharge (RR 11.46 [95% CI 1.65–79.61]). The specificity was 99% (eTable 3). Due to inclusion of only one study, heterogeneity could not be calculated. Results of the GO-FAR and PIHCA score are shown in Fig. 3.

Discussion

In this systematic review and meta-analysis, we investigated the concept, measures and application of medical futility regarding CPR after IHCA in clinical routine. We included 30 studies in the qualitative review and 11 in the meta-analysis. Aside from theoretical articles from the field of medical ethics, we found only few clinical definitions of futility regarding CPR and no international consensus including specific definitions or criteria that allow for concrete implementation in clinical practice. Still, several studies proposed different pre-arrest objective risk scores for the definition of futility[44,52] or to assess extremely low chance of survival (with favorable neurologic outcome, i.e. CPC 1 or CPC 1 to 2).[4,24,28,42,47–49] In meta-analyses, these four risk scores, i.e. PAM index, PAR score, GO-FAR score and PIHCA score, were associated with in-hospital mortality and – in the case of the GO-FAR and PIHCA score - in-hospital mortality and poor neurologic outcome defined as CPC 1 and CPC 1 to 2, respectively. Several findings of this review need further discussion.

First, we found a wide variation in definitions of futility, which were mostly either unspecific or limited to certain clinical conditions. In line with a systematic review on medical futility without focus regarding resuscitation[53] and current opinion of leading experts on the topic,[54] none of the studies in our review reported a definition including specific and well-defined criteria that would allow identification of patients

Table 1 – Summary of the studies included in the meta-analysis.

Authors	Study Purpose	Country	Participants	Design	Methods	Definition of Futility	Outcomes and Measures	Results
George et al. 1989[24]	To evaluate pre-arrest factors potentially predictive for survival after CPR for IHCA and devising a multifactorial scoring system, the Pre-Arrest Morbidity (PAM) Index, to evaluate pre-arrest morbidity in individual patients.	USA (Tennessee)	n = 140, patients receiving CPR after IHCA (65% men, age 18–92). Cardiac arrest is defined as acute circulatory failure for which both chest compression and artificial ventilation were initiated.	Prospective cohort study	Consecutive hospitalized patients undergoing CPR between July 1 through December 31, 1985 were prospectively identified. Data were collected through review of medical records and telephone interviews with survivors after 3 months. For comparison, data of hospitalized patients who died within the same six-month follow-up period but who did not receive CPR were also recorded.	Patients with a PAM score > 8 would not be expected to survive.	**Outcome:** Immediate success of CPR (restoration of pulse and maintenance of a systolic blood pressure for at least one hour without chest compression), survival to discharge and long-term survival at 3-month follow-up. **Measures:** Review of medical records concerning clinical characteristics before, during and after the resuscitation; telephone interviews with survivors 3 months after the arrest.	**Pre-arrest factors** associated with in-hospital mortality after CPR: hypotension, azotemia, age $\geq$ 65 years. The following cut-off values of the PAM score were defined for identifying extremely low likelihood of long-term survival: PAM score $\geq$ 7: less than 15% survived to discharge/were still alive 3 months later; PAM score > 8 (n = 24): none of these patients survived to discharge. When PAM score and other pre-arrest factors (azotemia, hypotension, and congestive heart failure) were assessed in a multivariate analysis, only PAM was significantly associated.
Ebell et al. 1997[26]	To evaluate the three clinical risk scores PAM index, PAR score, and the APACHE III score regarding their ability to predict survival to discharge after in-hospital CPR.	USA (Michigan and Illinois)	n = 656, inpatients of three hospitals with CPR after IHCA. Exclusion: observed IHCA, no documentation of CPR measures.	Retrospective cohort study	Medical records available during the first 24 hours after hospital admission of all inpatients who had received CPR after an IHCA were reviewed and APACHE III, PAR, and PAM scores were calculated.	none	**Outcome:** Survival to discharge after CPR for IHCA. **Measures:** APACHE III, PAM and PAR score rated based on medical records, demographic, clinical, and laboratory variables from medical records.	5.3% (n = 35) of patients survived to discharge (37.8% initially). None of the three clinical risk scores could effectively discriminate between survivors and non-survivors (neither immediate survival nor survival to discharge). This might be due to low statistical power caused by the small number of survivors. APACHE III did not discriminate. PAM: Only 11 of 656 patients had scores > 8, none of whom survived to discharge. PAR: 131 patients with scores > 8, 6 survived to discharge. Patients identified by the PAR score as non-survivors to discharge had a survival rate of 4.6%, not significantly different from the overall survival rate of the study population of 5.3%.
O'Keefe & Ebell 1994[43]	To compare the PAR score and PAM index regarding their ability to predict non-survival after CPR for IHCA.	Ireland	n = 274, inpatients of all wards who had received CPR after IHCA over a 2-year period, average age 70.1 years.	Retrospective cohort study	Medical records of inpatients who had received CPR after IHCA were reviewed. PAR and PAM were calculated based on the most recent data prior to cardiac arrest. Both a priori (based on the original publications) and post hoc (based on data of the current study, specificity set at 100%) cut-off values were applied.	none.	**Outcome:** Survival to discharge after in-hospital CPR for IHCA. **Measures:** Retrospective review of medical records regarding demographic, clinical and laboratory data, main diagnoses, daily medications, and survival to discharge.	Twenty-five (9.1%) survived to discharge. A priori cut-off values (>8 for both PAR and PAM) identified only few of the non-survivors: PAR identified 24 and PAM detected only 5 with a sensitivity of 9.6% (PAR) and 2% (PAM). Post hoc cut-off values set at 100% specificity detected 59 (PAR) and 23 (PAM) patients with a sensitivity of 23.7% (PAR) and 9.2% (PAM).

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Table 1 (continued)

Authors	Study Purpose	Country	Participants	Design	Methods	Definition of Futility	Outcomes and Measures	Results
Bowker et al. 1999[41]	To evaluate the usefulness of the morbidity scores PAM, modified PAM index and PAR score in predicting unsuccessful/futile CPR.	England	n = 264, consecutive adult patients who had received CPR after IHCA (59% men). Exclusion: OHCA, previous cardiac arrest, no CPR.	Prospective cohort study	Rating of PAM, modified PAM index and PAR score based on information in medical records.	none	**Outcome:** Survival after CPR. **Measures:** Pre-arrest morbidity score (PAM), prognosis after resuscitation score (PAR), modified PAM index (MPI).	Cut-off values indicating zero chance of survival and proportion of patients with respective cut-off value: PAM > 6 (17.8%), PAR > 7 (25.8%), MPI > 6 (20.1%). Sensitivity of scores: PAM 20%, PAR 29%, MPI 22%; combination of all three 42%. Each score identified a different subgroup of patients for whom CPR was unsuccessful with little overlap between the scores. While 100 of these patients were detected by one or more scores only 21 were identified by all three scores.
Ohlsson et al. 2014[46]	To evaluate the predictive performance of the PAM and PAR score regarding survival to discharge of patients receiving CPR after IHCA and to identify new clinically useful parameters.	Sweden	n = 278 (61.3% male, mean age 70.1); inclusion: inpatients who had received CPR after IHCA, 18 years or older; exclusion: OHCA.	Retrospective cohort study	Medical records were screened including all cases of IHCA who were part of a cardiac arrest registry at Skåne University Hospital in Sweden between 2007–2010.	none	**Outcome:** survival to discharge. **Measures:** Variables included in the PAM and PAR score, as well as additional clinical variables such as acute and chronic clinical diagnoses.	A PAR score > 5 was associated with a more than 8-fold increase in the risk of non-survival to discharge. The specificity of both scores increased with elevated scores, PAM- and PAR-scores > 5 and above had a specificity > 90%, which can be helpful to identify patients with the highest risk of failure to survive IHCA. Patients with ST-elevated myocardial infarction (STEMI), with cardiac monitoring and shockable rhythm had a higher likelihood of survival to discharge. Patients with malignancies and dependent functional status were less likely to survive. Many other severe comorbidities, such as chronic heart failure, chronic obstructive pulmonary disease, peripheral artery disease, chronic kidney disease, chronic cerebrovascular disease and diabetes mellitus, were not significantly related to reduced survival. Acute conditions such as acute renal failure, acute stroke, acute heart failure and sepsis were also not significantly associated.
Ohlsson et al. 2016[4]	To validate the "Good Outcome Following Attempted Resuscitation" (GO-FAR) score in patients in a Swedish hospital who received CPR after IHCA.	Sweden	n = 278 (61.3% male, mean age 70.1); inclusion: inpatients who had received CPR after IHCA, 18 years or older; exclusion: OHCA	Retrospective cohort study	Medical records were screened including all cases of IHCA who were part of a cardiac arrest registry at Skåne University Hospital in Sweden between 2007–2010.	Less than 3% chance of survival of CPR with poor neurologic outcome (CPC $\geq$ 2) or death until discharge.	**Outcome**: Survival to discharge with good neurologic outcome (CPC = 1) **Measures**: Variables of the GO-FAR score: Neurologically intact at admission, major trauma, acute stroke, metastatic/hematologic cancer, septicemia, medical noncardiac diagnosis, hepatic insufficiency, admitted from skilled	Overall survival to discharge independent of neurological function was 20.2%; 78% of the survivors had CPC = 1 and survival to discharge with CPC = 1 was 15.7%. The AUC for the GO-FAR score was 0.85. Patients in the group with low or very low probability of survival

Table 1 (continued)

Authors	Study Purpose	Country	Participants	Design	Methods	Definition of Futility	Outcomes and Measures	Results
							nursing facility, hypotension / hypoperfusion, renal insufficiency / dialysis, respiratory insufficiency, pneumonia, age.	had a likelihood of 2.8%, whereas the groups with average and above average probabilities had likelihoods of 8.2% and 46% for good neurological outcome.
Thai & Ebell 2019[47]	Prospective validation of the Good Outcome Following Attempted Resuscitation (GO-FAR) score for IHCA prognosis.	USA (all states)	n = 62,131 inpatients in 386 hospitals (58.3% male, mean age 65.3 years); inclusion: initial IHCA, 18 years or older, assessment of CPC at discharge, all 13 GO-FAR predictor variables documented.	Retrospective cohort study	Medical data of patients hospitalized experiencing IHCA between 2010 and 2016 were extracted.	Less than 3% chance of survival of CPR with poor neurologic outcome (CPC $\geq$ 2) or death until discharge.	**Outcome**: survival to discharge with good neurologic outcome (CPC = 1) **Measures**: Variables of the GO-FAR score: Neurologically intact at admission, major trauma, acute stroke, metastatic/hematologic cancer, septicemia, medical noncardiac diagnosis, hepatic insufficiency, admitted from skilled nursing facility, hypotension / hypoperfusion, renal insufficiency / dialysis, respiratory insufficiency, pneumonia, age; hospital size, having residents or interns, ownership type.	The GO-FAR score had similar discrimination, calibration, and classification accuracy as in the original study. Survival rates were somewhat higher due to a secular increase in survival of IHCA. The score performed similarly in hospitals of different sizes, with and without residency training programs, and with different ownership structures. The GO-FAR score accurately classifies patients into risk groups based on their likelihood of survival to discharge with a good neurologic outcome following the occurrence of IHCA.
Rubins et al. 2019[48]	To validate the utility of the GO-FAR score by retrospectively predicting prognosis after IHCA arrest in a US trauma center.	USA (Minnesota)	n = 403 (65.5% male, mean age 60.3 years); inclusion: pulseless IHCA, 18 years or older, initial cardiac arrest; exclusion: OHCA, DNR orders and stopped, subsequent cardiac arrest.	Retrospective observational study	Two authors independently calculated the GO-FAR score for each included case from the electronic health record between 2009 and 2018. The lead author reconciled any differences.	Less than 3% chance of survival of CPR with poor neurologic outcome (CPC $\geq$ 2) or death until discharge.	**Outcomes**: survival to discharge, survival to discharge with good neurologic outcome (CPC = 1) **Measures**: Variables of the GO-FARscore: Neurologically intact at admission, major trauma, acute stroke, metastatic/hematologic cancer, septicemia, medical noncardiac diagnosis, hepatic insufficiency, admitted from skilled nursing facility, hypotension / hypoperfusion, renal insufficiency / dialysis, respiratory insufficiency, pneumonia, age; timing of IHCA.	Overall survival to discharge was 33.0%; survival to discharge with good neurologic outcome was 17.4%. In the below average survival group calculated by the GO-FAR score (n = 150), only 5.3% survived to discharge with CPC = 1, significantly fewer than in the average (22.5%) or above average (34.1%) groups. GO-FAR score calculated at the time of admission correlated with survival to discharge with good neurologic outcome (AUC 0.68), therefore, the GO-FAR score can estimate the probability that a patient will survive to discharge with good neurologic outcome after an IHCA at time of admission.
Piscator et al. 2018[28]	External validation of the GO-FAR score predicting neurologically intact survival after IHCA in a population-based setting.	Sweden	n = 717 patients (mean age 72 years) / complete cases n = 523 (62% male, mean age 71 years); inclusion: IHCA (=patient who is unresponsive with apnea), 18 years or older.	Retrospective cohort study	Patients were identified through review of electronic patient records of the Swedish Cardiopulmonary Resuscitation Registry between 2013 and 2014.	Less than 3% chance of survival of CPR with poor neurologic outcome (CPC $\geq$ 2) or death until discharge.	**Outcome**: survival to discharge with good neurologic outcome (CPC = 1) **Measures**: Variables of the GO-FAR score: Neurologically intact at admission (GCS = 15), major trauma, acute stroke, metastatic / hematologic cancer, septicemia, medical noncardiac diagnosis, hepatic insufficiency, admitted from skilled nursing facility, hypotension / hypoperfusion, renal insufficiency / dialysis, respiratory insufficiency, pneumonia, age; gender, race, CA characteristics, hospital location.	22% of the cohort survived with good neurologic outcome. In below average survival groups, 4% survived with good neurologic outcome, compared to average and above average survival groups (32%). In complete case analysis (523 cases) AUC was 0.82 indicating good discrimination. The GO-FAR score has satisfactory discrimination, but assessment of the calibration shows that neurologically intact survival is

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Table 1 (continued)

Authors	Study Purpose	Country	Participants	Design	Methods	Definition of Futility	Outcomes and Measures	Results
								systematically underestimated.
Ebell et al. 2013[27]	To develop and validate an economical pre-arrest point score that can identify patients unlikely to survive CPR after IHCA neurologically intact or with minimal deficits.	USA (all states)	n = 51,240, 58.3% men, mean age 65 years. Inpatients of 366 hospitals with CPR after IHCA. (Patients with previous DNR orders not included).	Get With the Guidelines–Resuscitation registry data set of 51,240 inpatients of 366 hospitals.	Data was divided into training (44.4%), test (22.2%), and validation (33.4%) data sets, multivariate methods to select the best independent predictors of good neurologic outcome based on: several candidate decision models, use of test data set to select the model that best classified patients as having a very low (<1%), low (1%-3%), average (>3%-15%), or higher than average (>15%) likelihood of survival after in-hospital CPR for IHCA with good neurologic status. The final model was evaluated using the validation data set.	CPR is unlikely to lead to long-term, neurologically intact survival. GO-FAR score $\geq$ 14 (low 1–3%, very low < 1%).	**Outcome:** Survival to discharge after in-hospital CPR for IHCA with good neurologic status based on a Cerebral Performance Category (CPC) score of 1. **Measures:** variables of the GO-FAR score.	Overall rate of survival to discharge with a CPC score of 1: 10.4%. Determination of four categories estimating a patient's chance of survival with good neurological outcome as above average (>15%), average (>3% – 15%), low (1–3%) or very low (<1%). **Proportion of futile patients:** The GO-FAR score identified 9.4% of patients as having a very low likelihood of good outcome after CPR (<1%) and another 18.9% as having a low likelihood (1–3%). The GO-FAR score identified 28.3% of patients as having a low or very low likelihood of survival to discharge with good neurological outcome.
Piscator et al. 2019[49]	Development of the PIHCA score, a new pre-arrest prediction model of favorable neurological survival following IHCA.	Sweden	n = 717 patients (mean age 72 years) / complete cases n = 523 (62% male, mean age 71 years); inclusion: IHCA (=patient who is unresponsive with apnea), 18 years or older.	Retrospective cohort study	Data was based on a previous validation of the GO-FAR score (Piscator et al, 2018), redefining and reducing predictor variables resulting in a model of 9 predictors. The likelihood of favorable neurological survival was categorized into very low (<1%), low (1–3%) and above low (>3%).	Very low likelihood (<1%) or low likelihood (1–3%) of favorable neurological survival	**Outcome**: favorable neurological survival at discharge (CPC 1–2) **Measures**: Chronic comorbidity (Charlson Comorbidity Index), neurologically intact at admission, septicemia, medical noncardiac diagnosis, hypotension / hypoperfusion, renal insufficiency / dialysis, respiratory insufficiency, pneumonia, age.	The PIHCA score had an AUROC of 0.81 and satisfactory calibration. Forty-two percent of patients with above low chance of survival (>3%) and 3% with very low/low chance of survival ($\leq$3%) in the PIHCA score showed favorable neurological outcome. With a cut-off of 3% likelihood of favorable neurological survival, sensitivity was 99.4% and specificity 8.4%; predictive value for classification into $\leq$ 3% likelihood of favorable neurological survival was high (97.4%) and false classification into $\leq$ 3% likelihood of favorable neurological survival was low (0.6%).

The Abbreviations: CPR, cardiopulmonary resuscitation; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; PAM, Pre-Arrest Morbidity index; PAR, Prognosis After Resuscitation score; APACHE, Acute Physiology and Chronic Health Evaluation score; GO-FAR, Good Outcome Following Attempted Resuscitation score; PIHCA, Prediction of Outcome for In-Hospital Cardiac Arrest score; CPC, Cerebral Performance Category; DNR, do not resuscitate; AUROC, area under the receiver operating characteristic curve.

in whom the chance of futile CPR would be high in clinical practice. However, two studies used clinical risk scores and chose a specific cut-off to determine futility.[44,52] While multiple theoretical articles from the field of medical ethics describe specific concepts of medical futility, researchers closer aligned to clinical practice often emphasize the difficulty of determining and implementing such concepts.[15,54–57] In public and academic discussions about futility, multiple fundamental issues have been raised that hinder an international consensus definition. These include ethical questions and concerns, societal values, cultural beliefs, legal challenges, and clinicians' responsibilities.[9,15,54,58]

So far, the most promising approach to evaluate quantitative futility was based on objective risk scores, i.e., the GO-FAR and PIHCA score regarding expected in-hospital mortality and neurological outcome. Such an approach to define futility *quantitatively* requires the definition of a specific threshold below which CPR would be assumed futile and a clear and clinically meaningful definition of "good outcome".[11] Yet, determining such a cut-off value for use in clinical practice has ethical and clinical challenges and may depend on societal and patient factors and perspectives as well as preferences of patients and families.[55] There may be differences in the perception what the best cut-off should be to define futility. When asked about their estimations of survival of patients in whom they perceived CPR to be futile, several physicians reported probabilities of over 5% and over 10%.[15,45] Further, the two existing clinical risk scores additionally considering neurological outcome differ in their definition of good neurologic function, i.e. CPC 1 in the GO-FAR score vs. CPC 1 to 2 in the PIHCA score.[10,28] Additionally, other meaningful clinical outcomes such as quality of life, self-reliance and severe health impairments, e.g., organ failures, need to be considered and incorporated into the concept of futility regarding CPR.

The concept of *qualitative futility* centers the patient's quality of life instead of quantitative parameters. This approach was only mentioned by two studies in our review.[45,51] If applied consequently, this approach requires an evaluation of patients' subjective quality of life as well as their idea of a meaningful and fulfilling life, considering the potential adverse neurological consequences of CPR. Moreover, the latter seems to become even more prominent with advanced and invasive life-prolonging interventions, such as extracorporeal membrane oxygenation (ECMO), as these can be associated with neurological complications.[59] Still, the potential influence of physicians' value judgments, beliefs and assumptions about the patient's quality of life and the limited number of studies regarding the impact of invasive life-prolonging measures in intensive care on short- and long-term outcome make decisions on qualitative futility challenging in routine care.[15,54–55,57,59]

Only four studies[39,40,44,52] assessed the code status in patients in whom resuscitation was determined futile. The rates of DNR orders in these studies varied due to the high heterogeneity of patient samples, definitions and assessments of futility, making interpretation difficult. While Teno et al.[39] explicitly stated that surrogates and patients participated in decision-making, it is unclear if DNR orders in the other three studies[40,44,52] were unilaterally implemented by physicians or discussed with patients and/or surrogates.

In our meta-analyses, we included 11 studies that applied clinical risk scores to estimate outcome of CPR and reported rates of survival to discharge (with good neurologic outcome) for each individual score.[4,24,41,43,26–28,46–49] The PAM index and a modified version

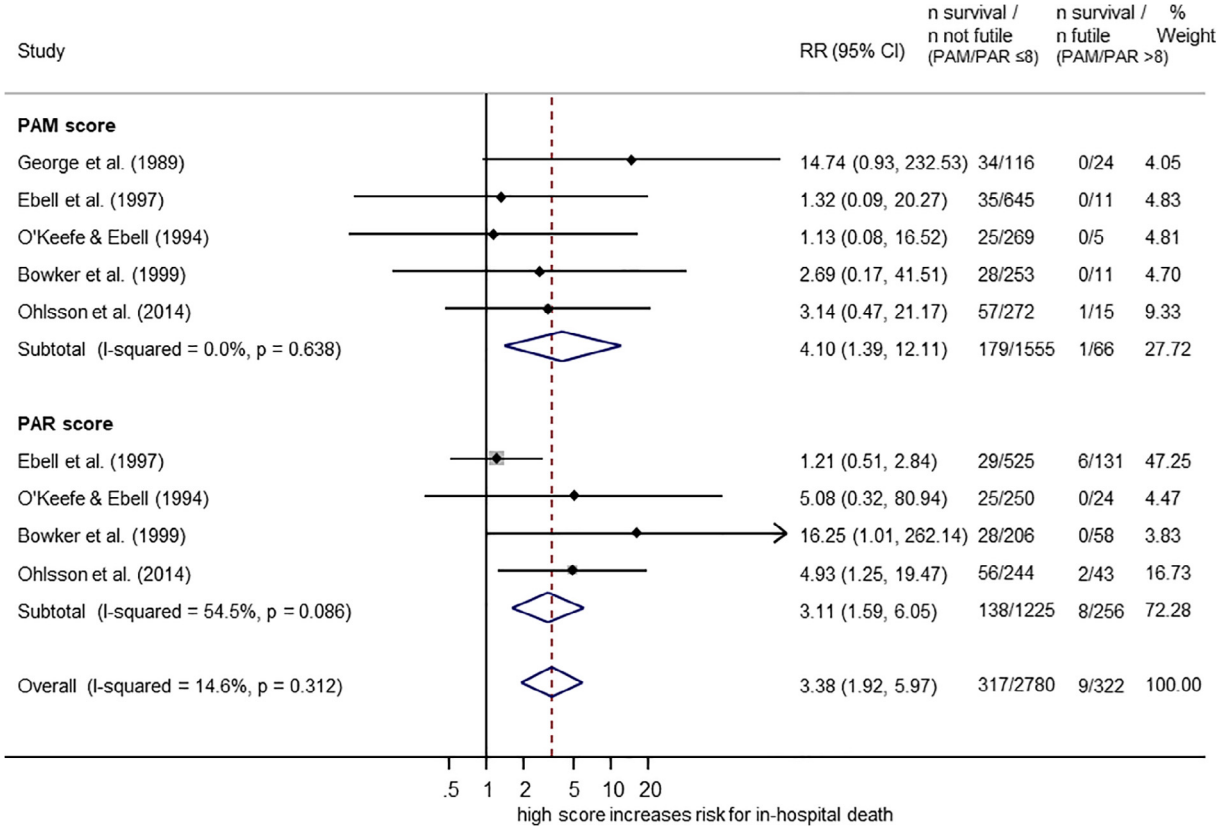

Fig. 2 – Forest plot showing the association of the PAM and PAR score and risk of in-hospital death.

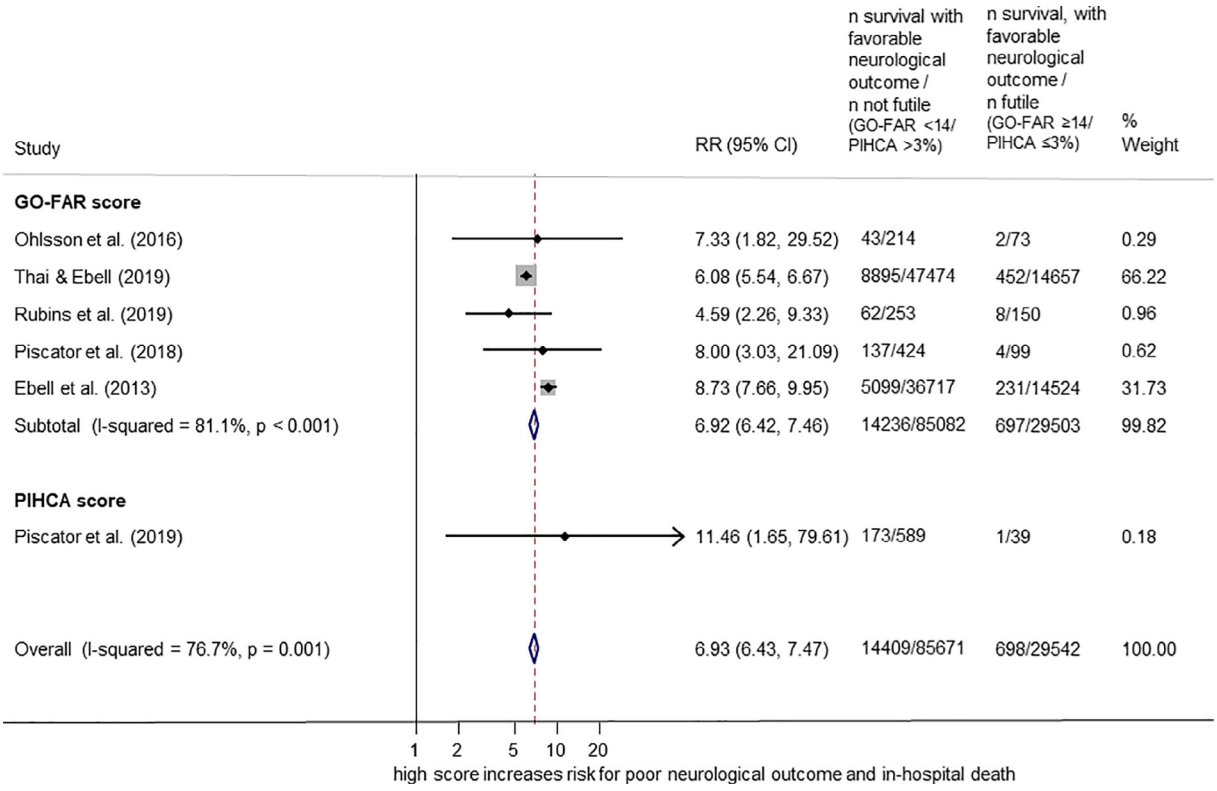

Fig. 3 – Forest plot showing the association of the GO-FAR and PIHCA score and risk of survival with impaired neurological outcome or in-hospital death.

named the PAR score were developed four decades ago, about three decades after the invention of CPR.[60] Surprisingly, we only identified five studies evaluating these scores in relation to survival rates[24,26,41,43,46] and two further studies in relation to rates of DNR orders.[25,44] Further, the studies used different cut-off scores for determining high risk of in-hospital death after CPR. In our meta-analysis, both the PAM and PAR score were associated with in-hospital mortality, albeit with a lower predictive value than the newer GO-FAR score and its derivative, the PIHCA score. Most predictors of the PAM index are variables that were independently associated with mortality following CPR in a previous primary study[61] plus factors deemed relevant by the authors[24] and the PAR score is based on a meta-analysis of 14 studies.[62] The GO-FAR score was developed based on multivariable analyses of a dataset of about 50,000 inpatients with IHCA.[1,27] Further, the GO-FAR and PIHCA score predict survival with good neurologic outcome, which is defined as Cerebral Performance Category (CPC) 1, indicating good cerebral performance, in the GO-FAR score and as CPC 1 to 2 with 2 indicating moderate cerebral disability, in the PIHCA score. These aspects might have contributed to their better performance in our analysis.

Due to the PAM and PAR scores' above-mentioned limitations, we suggest focusing on the GO-FAR and PIHCA score in future research. Further studies are needed to validate the GO-FAR and/or PIHCA score regarding their prognostic accuracy. As a next step, implementation of these scores in clinical practice is needed. Potential benefits and short-comings of using clinical risk scores for decision-making regarding code status need to be assessed, e.g., does decision-making change due to risk scores or is it coherent with clinical impression. Although clinical scores are never perfectly accurate in their prediction of outcome, they may reduce the influence of subjective factors that should not contribute to determining futility such as physicians' individual values and attitudes. Risk scores may help guide physicians in the difficult task of futility assessment to make this evaluation more objective, transparent, and hopefully reliable especially when physicians are still unexperienced. According to the online registration platform ClinicalTrials, there is currently one large randomized trial comparing code status discussions based on a checklist and risk assessment of futility using the GO-FAR score and the Clinical Frailty Scale with usual care (https://clinicaltrials.gov/ct2/show/NCT03872154).

Conclusions

In summary, although in-hospital cardiac arrest occurs in about 2–3% of hospitalized patients and code status discussions and decisions are an integral part of clinical practice, there is only little research on consensus definitions of medical futility. While most clinicians would agree that there is a relevant proportion of patients in whom CPR is likely to be futile, our review found no established definitions of futility for use in clinical practice. International consensus regarding the definition of futility is lacking and tools for its assessment could improve objective code status discussions with patients. Communication about medical futility holds the potential of empowering patients to make informed decisions that are in alignment with their goals of care, avoiding unwanted physical and emotional suffering for them and their relatives, which may come along with unwanted life-sustaining measures and treatments in situations without realistic prospects for a desirable recovery in the individual case. A definition, criteria and measures suitable for the implementation of

scoring systems to determine the likelihood of futility in specific clinical scenarios need to fulfill several requirements regarding acceptance, feasibility, and prognostic value, among others. Two recently developed clinical risk scores, the GO-FAR and PIHCA score, showed promising predictive values. However, further studies are needed to evaluate the implementation of such concepts and their assessments in clinical practice.

CRediT authorship contribution statement

Katharina Beck: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing - original draft Writing - review & editing. **Alessia Vincent:** Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft. **Hasret Cam:** Investigation, Methodology. **Christoph Becker:** Conceptualization, Funding acquisition, Writing - review & editing. **Sebastian Gross:** Writing - review & editing. **Nina Loretz:** Writing - review & editing. **Jonas Müller:** Writing - review & editing. **Simon A. Amacher:** Writing - review & editing. **Chantal Bohren: Writing – review & editing**. **Raoul Sutter:** Writing - review & editing. **Stefano Bassetti:** Writing - review & editing. **Sabina Hunziker:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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Appendix E

Study V

Vincent, A., Semmer, N. K., Becker, C., Beck, K., Tschan, F., Bobst, C., Schuetz, P., Marsch, S., & Hunziker, S. (2021). Does stress influence the performance of cardiopulmonary resuscitation? A narrative review of the literature. *Journal of Critical Care, 63,* 223–230. https://doi.org/10.1016/j.jcrc.2020.09.020

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Does stress influence the performance of cardiopulmonary resuscitation? A narrative review of the literature

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ABSTRACT

Cardiopulmonary resuscitation represents a major physical and psychological challenge for all involved health care workers because survival of the patients is closely related to the timely and accurate actions of rescuers. Consequently, rescuers may experience high levels of acute mental stress. Stress, in turn, may influence attentional resources and distractibility, which may affect the quality of resuscitation. This narrative review summarizes the current state of research concerning the influence of stress on resuscitation performance. Peer-reviewed studies retrieved in scientific databases were eligible. We found that rescuers experience high levels of stress and some associations of higher levels of stress with lower resuscitation performance. Finally, few interventional studies assessed whether interventions aiming at reducing levels of stress may have a beneficial effect on resuscitation performance, but results are variable. Although the mechanisms linking stress to performance of emergency teams are still not fully understood, factors such as individual experience and self-confidence of rescuers, gender composition and hierarchy within resuscitation teams may play an important role. This review provides a targeted overview of how stress can be defined and measured, how it may influence emergency situations such as a cardiopulmonary resuscitation, and which interventions have the potential to reduce overwhelming stress.

1. Introduction

A cardiopulmonary resuscitation (CPR) is a dramatic challenge for all involved healthcare professionals, as a patient's survival closely depends on immediate initiation and accurate performance of resuscitation efforts. As a consequence, rescuers may experience high levels of acute mental stress. There is good evidence demonstrating that stress potentially reduces attentional resources [1,2], increases distractibility [3-5] and thus may impair resuscitation performance [6-8]. At the same time, it is well known that in challenging situations and during demanding tasks people often have extraordinary capabilities to protect their primary activities from decrements due to stress [1,9]. This review focuses on mechanisms and interventions associated with stress and performance in emergency situations, such as CPR. Towards this aim, we identify a working definition of stress, methods of measuring stress and review existing evidence on the relationship between measures of stress and performance, particularly in critical situations such as CPR. We also consider alternative explanations for these relationships and identify questions that require further exploration. Literature is based on a search of terms in scientific databases drawn from a set of key articles and initial keywords such as stress, distress, CPR, cardiopulmonary resuscitation and performance.

2. What is stress and how do we measure it?

The term *stress* is broadly used to describe a physiological and emotional response to a situation, either defined subjectively [12] or as an objective pattern of hormonal responses [10,11].

Stress can be defined as a primarily positive (eustress) or negative experience (distress) [10], or a combination of both [12]. For the purpose of this review, we focus primarily on distress. However, the consequences of distress are not necessarily always negative [13], but can also induce positive outcomes [13,14].

Although stress characterizes most emergency situations, there is no gold standard for stress measures. Therefore, different measures are used, the most common being biochemical, physiological and

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psychological parameters. Typical biochemical stress measures are adrenal stress hormones, such as cortisol, which can be measured in the blood stream, urine or saliva, or adrenalin and noradrenalin, which however show higher variability. Common physiological parameters are heart rate, which increases during stress, and heart rate variability, which is defined as the standard deviation of all regular RR intervals on the ECG [15,16] and typically decreases during acute mental stress [17-19]. Psychological parameters often use self-report measures, e.g. the Uwist Mood Adjective Checklist [20], the state-version of the Spielberger State-Trait Anxiety Questionnaire (STAI [21]) and its short form ISAT [22], and the Geneva Emotion Wheel [23] which has successfully been used to capture emotions in resuscitation situations [6]. Also, scenario perceived stress during a CPR scenario was best represented by a combination of the two distinct items: feeling "stressed" and feeling "overwhelmed" resulting in a "stress-overload" index [6].

The complexity of different stress parameters in acute emergency settings is illustrated by a clinical study examining different stress measures over the course of a simulated resuscitation [24]. Self-reported stress showed the strongest association with performance, while physiological measures, such as heart rate, showed an inverse association with performance. This may be due to the physical activity, limiting its value as a mental stress marker in this acute setting [24]. In contrast, better correlations of self-reported stress measures and biological indicators, such as heart rate and cortisol, have been described in the setting of the operating room [22].

Recently, ECG recordings have been used as a new physiological stress measure. A study using simulated cardiac arrest recorded ECGs of healthy medical students as rescuers [25]. These ECGs showed a stress-induced increase in heart rate and decrease of heart rate variability, as well as dynamic alterations such as ST-segment or T-wave alterations, normally seen in patients with ischemic heart disease [25]. Similar patterns were observed in a study combining physiological and psychological challenges, in which the combination of both challenges led to significant attenuation of T-wave amplitude [26]. Therefore, stress may be measured by ECG focusing on ST-segment or T-wave alterations.

Which type of measure best represents mental stress remains unclear and each measure has unique, inherent shortcomings.

3. Stress during cardiopulmonary resuscitation

Different investigators documented considerable stress levels in response to CPR situations using different measures to quantify stress. Table 1 shows an overview of recent clinical studies that investigated stress as the primary outcome. Most of these studies used a patient simulator to study the acute stress response of rescuers. While the stress response during simulation may somewhat differ from a real life situation, simulation provides a unique research venue that allows rigorous assessment of different stress parameters during emergency situations in a realistic, yet safe environment [6]. Still, in previous studies, resuscitation scenarios in high fidelity simulators were experienced as realistic and highly stressful by participants [27,28]. In addition, unlike actual emergency situations, a controlled, standardized experimental situation can be simulated and the effect of different interventions can be compared.

All studies reported an increase in stress during resuscitation situations. Two studies assessed biological markers [29,30], three used self-report [31-33], and three investigated both biological markers and self-report [34-36]. In one study, cortisol was associated with both feeling stressed and feeling challenged [34]. Research considering biological stress markers during resuscitation or simulated emergency situations reported increased cortisol levels [29,34,36], increased heart rate and/

Table 1
Studies investigating stress as an outcome.

Reference	Emergency situation	Stress assessment		Performance measurement	Participants	Study design	Main findings
		Self-report	Biological				
Morgan & Westmoreland [31]	Cardiac arrest	Self-report (1 question)	NA	NA	41 junior doctors	Questionnaire	73% of the doctors felt stressed attending a cardiac arrest
Scott, et al. [32]	Cardiac arrest	Self-report (1 question)	NA	NA	96 residents	Questionnaire	52.1% of residents felt stressed when participating in cardiac arrests, 47.9% felt inadequately trained
Hayes et al. [33]	Cardiac arrest	Self-report (4 questions)	NA	NA	289 residents	Questionnaire	52.1% of residents felt prepared to lead a cardiac arrest team, 55.3% worried about making errors, and 49.3% felt inadequately trained
Quilici et al. [30]]	ACLS or real life emergency room	NA	Heart rate, blood pressure	NA	18 residents	RCT, simulation vs. real life	Higher stress during simulation compared to real life scenario
Bong et al. [29]	Simulated emergency situations	NA	Heart rate, salivary cortisol	NA	27 gastroenterology physicians	RCT, simulation-based vs. interactive-education training	Higher stress responses in terms of heart rate and cortisol after simulation-based training
Harvey et al. [34]	Simulated trauma resuscitation	Cognitive appraisal and STAI	Salivary cortisol	NA	13 residents	RCT, high or low stress situation	Subjective appraisal of threat and challenge associated with cortisol response
Daglius Dias et al. [35]	Simulated ACLS scenarios	STAI-s	Heart rate, systolic blood pressure, salivary a-amylase, interleukin	NA	18 residents	Prospective observational study	Acute stress response did not differ between simulation or real-life setting, stress was higher in both groups after emergency situation
Ghazali et al. [36]	Simulated emergency situation	STAI, SOM-Scale, IES-R, PCLS	Heart rate, heart rate variability, salivary cortisol	NA	48 EMS team members with less than 7 years experience	Observational	All stress measures increased during simulation and decreased during debriefing, but the different stress parameters did not correlate with each other

RCT, randomized controlled trial; ACLS, advanced cardiac life support; ATLS, advanced trauma life support; STAI, state-trait anxiety inventory; VAS; visual analogue scale; NA, not available.

or decreased heart rate variability [29,30,35,36], arterial/systolic blood pressure [30,35], and salivary amylase and interleukin-1β [35]. Whereas one study demonstrated higher stress during simulation than in the real life scenario [30], another study found all biological stress measures to increase in the real life scenario, and less in the simulation [35].

Focusing on self-report measures, descriptive studies showed that well beyond half of the participants felt stressed during resuscitation [31,32] and inadequately trained for the task [31-33]. Also, residents reported that they did not receive enough post-event debriefing or feedback [31,33]. Furthermore, self-reported anxiety was heightened after emergency situations [34-36].

The presented studies mostly focused on residents [30-35] and only two included senior physicians and other more experienced health care workers [29,36]. Therefore, the amount of stress experienced by more practiced resuscitators is under-investigated. Also, the different stress parameters were mostly uncorrelated [36], further strengthening the finding that stress parameters are not easily comparable [37,38]. Interestingly, one study found that the subjective appraisal of the situation was associated with the stress response [34]. Hence, if the scenario was appraised as a threat, cortisol and anxiety levels were higher. However, if the situation was appraised as a challenge, no association was found with stress response [34]. Nonetheless, it is evident that the resuscitation situation stresses rescuers on a psychological and physical level, at least in inexperienced rescuers.

4. Stress and performance: possible mechanisms

Acute stress reactions are often associated with mechanisms that entail momentary performance risks, due to the limited mental resources in a highly demanding situation [1,2]. Table 2 shows possible general mechanisms between stress and performance in different performance domains which are all relevant for CPR performance.

Performance becomes increasingly vulnerable if additional demands arise [9]. In the context of resuscitation, stress may lead to a loss of team perspective and favor only the individual perspective [40], or demonstrate shortcomings in the task-distribution of the team [40,41]. This neglect of certain aspects of the task only deteriorates overall performance if an important aspect of the task is neglected.

Still, people have been found to sustain performance under stressful conditions to a considerable extent [1,9]. Such performance-protecting strategies are more likely to succeed in highly practiced and thus automatized tasks [39], implying that less experienced professionals are more likely to get embroiled in a single and less central activity [9]. Thus, effects of stress are more likely to be found among the less experienced, such as medical students or residents. Conversely, very high levels of stress during emergencies would probably be required for finding effects of stress on performance among highly experienced medical professionals.

5. Does stress influence performance in resuscitation?

It has been shown that resuscitation has stressful effects that can be measured biologically and psychologically [34,36], and that stress has detrimental effects on general performance [42,43]. However, the question remains to which extent stress affects performance in CPR. Table 3 refers to studies that report performance outcomes: Table 3a reports three studies that describe results concerning only biological stress markers. Two studies report an increase in stress markers but no association between stress and performance during simulation [44,45]. Contrarily, the third study did find associations between performance, assessed by hands-on time, and electrophysiological parameters, such as heart rate, heart rate variability and tachycardia [25]. Especially resuscitators with ST-elevations showed significantly decreased performance [25]. Table 3b contains four studies that used self-report measures of stress. Three of them [6-8] found an association of stress with lower performance. The fourth study [46] showed that by inducing socio-emotional stress in the experimental group, values for self-reported mental demands, effort, time pressure, and frustration were higher than in the control group; there were no differences in performance, however. Note that participants were highly experienced and had received extended and repeated training [46]. Table 3c contains four studies using both self-report and biological stress markers [24,47-49]. One

Table 2
Possible mechanisms between stress and performance.

Performance domain	Effect of stress	Main findings
Attention allocation	Narrowing of attention	- Entails the danger of exclusively focusing on a single subtask and, therefore, disregarding potentially important information which is less salient in the task, e.g. tunnel vision [69]. - Can also lead to improved performance by supporting focus on the task [70].
	Premature closure	- Making decisions based on insufficient consideration of the information available [71].
	Impairment of information suppression	- Inability to suppress irrelevant information [3]. - Leads to increased distractibility and misjudging priorities [3-5]. - Non-systematic scanning of informational cues [71]. - Distracting information stems from external events internally generating intrusive thoughts, such as worrying about performance [72].
Memory	Facilitating effects	- Memory is enhanced for affect-laden aspects of the situation [65,66].
	Inhibiting effects	- Intense stress inhibits memory, especially regarding explicit as opposed to implicit information processing [43]. - Impairment of prospective memory (i.e. remembering an intention), which leads to forgetting an action that is planned for later, resulting in an error of omission [73,74]. - Impairment of retrieval of previously learned information, especially information learned under non-stressful conditions retrieved under stress [63,64].
Aftereffects of stress	Routine situations	- Routine and low-stress situations after a stressful situation are error prone [9,42,75].
	Low effort mode of control	- Following activities are carried out with less effort and less focused attention [1].
Learning	Learning under stress	- Information acquired under stress can also be retrieved more easily under stress [43]. - Training for stressful situations should include exposure to stressful conditions with gradually increasing intensity [75].
Social factors	Expectation states theory	- Leadership can be attributed or claimed on the basis of expectations, which may not represent an optimal allocation of roles, e.g., attributing a leadership role to a more senior team member, who is however less competent or experienced for the demanded task [76].
	Leadership to diminish stress	- Directive leadership, i.e. short and clear statements to specific team members help to optimize team performance, especially in ambiguous situations [77]. - The leader should "step back" in order to keep the overview [78] and only interfere if needed [40,41]. - Leadership should give opportunities to raise questions and concerns [79] to prevent and recognize errors [80]. - Training teams in coordination and leadership [81] may help to routinize teamwork and potentially lead to stress-reduction [78,82].

Table 3
Studies investigating performance as an outcome.

Reference	Emergency situation	Stress assessment		Performance measurement	Number of participants	Study design	Main findings
		Self-report	Biological				
a) Biological markers only							
Keitel et al. [44]	Simulated cardiac arrest	VAS on stress related items assessed but not analyzed	Salivary cortisol	Medical performance rated using checklist	34 medical students	RCT, rest, laboratory stress or emergency situation	Cortisol increased in both stress situations. Cortisol increases in the laboratory stress situation were positively related to medical performance, but cortisol in the simulated emergency situation was not. No correlation between VAS and performance was calculated.
Mueller et al. [45]	Simulated emergency	NA	Salivatory cortisol, salivatory amylase	Clinical performance rated using checklist	32 intensivists	RCT, classic training or crew resource management training	Significant stress response due to simulated emergency situation, which decreased after training; neither amylase nor cortisol were related to performance. No effect of type of training (CRM vs. classical medical training)
Tramer et al. [25]	Simulated cardiac arrest	NA	Heart rate, heart-rate variability, ST- and T-wave morphology	Hands-on time during CPR, first meaningful measure	126 medical students	Observational simulator study	Stress-induced increase in heart rate, decrease of heart rate variability and ST-elevations; heart rate and heart rate reactivity correlated with hands-on time.
b) Self-report only							
Hunziker, Laschinger, et al. [83]	Simulated cardiac arrest	Perceived stress on Likert scale	NA	Hands-on time	120 medical students	Observational	Clear increase in self-reported stress. Significant negative correlation between "stress/overload" and performance
Bjorshol et al. [46]	ACLS	Subjective workload, frustration, realism	NA	Quality of CPR	19 paramedic teams	RCT, with or without socio-emotional stress	Stress increased workload, frustration and realism; no effect of stress on performance. Note that participants were highly experienced, repeatedly trained (incl. simulation) and recertified in ALS; plus participants were explicitly instructed to deliver ALS.
Krage et al. [8]	Simulated cardiac arrest	Stressful vs. non-stressful CPR scenario	NA	Technical and non-technical performance scores	30 anaesthesiologists and anaesthesia residents	Simulator-based randomized cross-over study	During CPR with external stressors, non-technical performance declined. Also, the team's technical performance was related to the non-technical skills of the team leader only when stress was high.
Hunziker, Pagani, et al. [7]	Simulated cardiac arrest	perceived stress on Likert scale	NA	Hands-on time, time to start CPR, leadership	124 medical students	RCT, task focusing questions	A brief task focusing strategy decreased perceived stress without significantly affecting performance of rescuers. However, self-reported stress was associated with lower performance.
(c) Biological and self-report							
Hunziker, Semmer, et al. [28]	Simulated cardiac arrest	"Feeling stressed" and "overwhelmed" on Likert scale	Plasma cortisol, heart rate, heart rate variability	Hands-on time, time to start CPR	28 residents	Observational	Self-reported stress was the only predictor for low CPR performance; few significant correlations between various stress measures; heart rate was associated with better performance.
Geeraerts et al. [47]	Simulated cardiac (pre-) arrest	Numeric stress scale, peritraumatic stress inventory	Salivary amylase concentration	Quality of care, time to understand situation, to find right cause and to implement measures; Non-technical skills (ANTS)	27 residents	Observational	All stress parameters increased after simulation; no significant correlation between physiological/psychological stress parameters and technical or non-technical performance.
Lizotte et al. [49]	Simulated neonatal resuscitation	Anxiety questionnaire, 10-point scale	Salivary cortisol	NRP Advanced Megacode Assessment Form	42 residents	Observational	Survival and death scenario were randomized in different order. Performance, self-reported stress and cortisol levels before and after CPR did not significantly differ between the two conditions. Cortisol increased after CPR but was not associated with performance.
Piquette et al. [48]	Simulated emergency situation	STAI, Cognitive Appraisal Questionnaire, 10-point scale	Salivary cortisol	Ottawa GRS	54 residents	Observational	Control and high-stress scenarios led to significant stress responses among participant. Yet physiological and psychological stress and CPR performance did not differ between conditions.

RCT, randomized controlled trial; ACLS, advanced cardiac life support; ATLS, advanced trauma life support; STAI, state-trait anxiety inventory; VAS; visual analogue scale; NA, not available.

Table 4
Studies that use learning as an outcome.

Reference	Emergency situation	Stress assessment		Performance measurement	Number of participants	Study design	Main findings
		Self-report	Biological				
DeMaria et al. [50]	Simulated cardiac death	STAI	Heart rate	Written knowledge test, performance rated	20 medical students	RCT, with or without additional emotional stressor	In presence of an emotional stressor, state anxiety and heart rate were higher and rated performance was better; no differences were found in the knowledge test. Since performance was assessed 6 months later, the study assessed learning rather than performance.
Lima et al. [51]	ACLS	Stress scale	Pulse rate variation, blood pressure	Theoretical examination	17 physicians	Observational	Stress had a negative impact on the learning process and on efficacy of training. Measures were taken in connection with a test; it therefore is unclear whether the results reflect learning or test performance

RCT, randomized controlled trial; ACLS, advanced cardiac life support; ATLS, advanced trauma life support; STAI, state-trait anxiety inventory; VAS; visual analogue scale; NA, not available.

study found self-reported stress to be associated with lower performance; by contrast, higher heart rate was associated with better performance, defined as time elapsed until CPR was started. Cortisol was not associated with performance. Furthermore, the study found few associations between self-report, physiological, and biochemical stress markers [24]. The other studies found no correlation between the physiological and psychological stress markers and performance [47-49].

Table 4 is concerned with learning outcomes. De Maria et al. studied the effects of adding socioemotional stressors by having confederates intervene, with effects on learning as the primary outcome [50]. In comparison to a control group, participants in the experimental groups showed increased heart rate and state anxiety. Six months later, the experimental group showed superior performance in a similar scenario [50]. Further, Lima et al. investigated the effect of stress on grades in a theory test after training [51]. They assessed stress by self-report measures, asking about the perceived stress levels in nine different scenarios, such as stable and unstable tachycardia, acute myocardial infarction, and by physiological stress markers, such as blood pressure and heart rate, taken after a practical test. Higher heart rate, systolic blood pressure, and self-reported stress were associated with lower grades. Note that the performance outcome in this study is not practical performance but grades in a knowledge test [51].

In sum, elevations of stress markers are consistently reported in studies considering the effect of stress on performance in resuscitation. While most studies did not find biological stress markers to be associated with lower CPR performance, a higher heart rate showed conflicting results and was associated with both decreased [25] and enhanced resuscitation performance [24]. The mixed results concerning physiological markers such as heart rate indicate that physical activity during resuscitation may act as a possible confounder and is, therefore, not suitable as a stress marker. By contrast, all studies except for two [46,47] found performance impairments associated with higher self-reported stress; one exception refers to a study with highly experienced participants, who had been repeatedly trained and certified with regard to CPR [46]. The studies investigating stress and learning effects suggest that stress may potentially enhance performance in a comparable situation later on [50] but may inhibit performance regarding knowledge [51]. Taken together, it appears that subjective compared to biological stress parameters are more strongly associated with CPR performance. However, if perceived stress has a causal effect on performance or vice versa is largely left untested.

6. Stress and gender in CPR: is there a difference?

A recent line of research in medical students performing simulated resuscitations has focused on possible gender differences concerning performance and stress reactions that can arise during resuscitation. Female students have shown inferior performance during resuscitation than males [52]. Female-only teams demonstrated a longer delay before starting chest compressions, less hands-on time, and lower leadership performance compared to male-only teams [52]. Furthermore, female students showed fewer leadership statements when compared to their male counterparts [52,53], whilst having the same amount of knowledge and experience [53]. Also, female students tend to transfer leadership tasks to other team members in mixed gender resuscitator groups [52].

Studies concerning perceived stress during simulated cardiac arrest have also shown gender differences in medical students. For instance, female students reported higher anxiety and demonstrated higher heart rate and lower LF/HF ratio after an emergency situation [36]. Also, though simulated cardiac arrest causes stress for both men and women, women reported higher perceived stress, more negative emotions and less positive emotions than men [6]. Further, females showed more pronounced electrocardiogram alterations, such as a higher maximal heart rate, lower heart rate variability and more abnormalities in T-waves and ST-segments [25]. Similarly, stress parameters such as heart rate variability and tachycardia were associated with hands-on time in resuscitation performance even after adjustment for influencing factors such as gender, leadership designation and chest compression [25]. As these findings do not allow for causal interpretation, it remains unclear whether negative emotions and stress influence inferior performance in female resuscitators, or vice versa.

However, it has been shown that women have equal, in some cases even better, medical knowledge than men [54]. Furthermore, if female medical students receive a brief gender-focused intervention focusing on leadership instructions and self-perception of female rescuers, leadership skills can be significantly improved [59]. Considering the presented gender differences in stress and negative emotions, other research has shown gender differences indeed exist in global self-descriptions, but not in momentary ratings of emotions [55]. As stress and negative emotions have repeatedly been shown to be associated with lower performance, it might be worthwhile to develop interventions that target this gender difference, making female resuscitators aware of a possible bias towards their own stress perception and focusing on stress reduction.

Importantly, the studies regarding gender differences in CPR situations were done with inexperienced medical students. To assess whether these findings can be extrapolated to more experienced physicians, a recent observational study examined the relationship between gender of physician code leaders and measures of CPR quality in a retrospective, observational study including 1082 adult inpatients who suffered cardiac arrest and underwent CPR in two academic, urban hospitals in the US [56]. Within a subgroup of 227 resuscitations with an initial 5 min of CPR parameter data, female physician code leaders were two times more likely to achieve return of spontaneous rhythm (ROSC) and females did not do worse in regard to either chest compression rate, depth or fraction. Unfortunately, stress was not measured in this study. As the above mentioned study had a retrospective observational design, prospective interventional research is needed to prove causality. Still, based on the current evidence, we hypothesize that

future training focusing on leadership training in inexperienced female students may help to improve the differences between gender in regard to leadership.

7. Can we reduce stress and how does it influence performance?

The question arises whether a reduction of stress could influence resuscitation performance and whether such interventions exist, given the fact that stress has repeatedly been shown to impair performance in simulated resuscitation scenarios [6-8].

Leadership trainings have been found to effectively decrease stress levels and increase confidence while performing simulated resuscitation [59]. Further, an intervention focusing on leadership instructions versus technical instructions showed better overall CPR performance for the leadership instructions [60]. The group receiving leadership instruction demonstrated longer hands-on time, shorter time to start CPR and more leadership utterances with sustained effects at a 4-month follow-up [60]. Also, a systematic review considering stress and decision-making during resuscitation showed that cognitive aids, stress management training and mindfulness meditation improve non-technical skills such as decision-making [61]. Therefore, different interventions can reduce perceived stress and improve performance, but it is yet unclear if the reduction of stress in these interventions lead to improved performance or vice versa, or if the two are causally unrelated.

A single study examined the impact of a stress coping strategy on performance and stress during CPR [7]. This randomized controlled trial included an intervention in which medical students were instructed to ask two task-focusing questions when they felt stressed or overwhelmed by the situation ("what is the patient's condition?" and "what immediate action is needed?"). The intervention group demonstrated decreased stress in comparison to the control group, but no differences in CPR performance were shown [7]. However, participants were 4th year medical students and it is therefore unclear whether these stress-related outcomes may be different for more experienced personnel.

Due to the sparse research on this topic, more studies concerning stress-reducing interventions are needed, especially given the current knowledge of the negative effects of stress on performance in general [1,2] and during resuscitation [6-8]. By focusing on stress-reducing interventions in trainings for CPR, performance may be enhanced, especially for more inexperienced personnel.

8. Discussion and future directions

8.1. Main findings

The aim of this review was to demonstrate the experience of stress associated with resuscitation and the effects it has on its performance. Throughout this review, we have established a working definition of stress and shown methods of measuring stress with biological, physiological and self-report measures. Furthermore, we have shown that resuscitators often experience stress during CPR on a biological and psychological level [30-35]. Further, stress was reported to reduce aspects of general performance, such as narrowing the attention span [62] and impairing retrieval of previously learned information in non-stressful conditions [63,64], but also to protect performance by enhancing memory and retrieval in affect-laden situations [43,65,66] in simulation studies. Also, this review has shown that especially self-reported stress, but also physiological stress, is associated with lower CPR performance [6-8,25]. When considering gender differences, female students have shown inferior performance [52] and reported to be more stressed during CPR than male students [36] which was found to be negatively associated with each other [6], explaining female' worse performance. However, women have equal medical knowledge as men [54] and CPR performance can be improved with a gender-focused intervention [59]. There are many stress reducing interventions [5,57,58], yet to the best of our knowledge, only one intervention targeting stress reduction during CPR exists [7].

However, it was also found that stress experienced in CPR does not always lead to performance impairments [44-47], and that self-reported stress and biological stress measures often do not coincide [36-38]. First, teamwork is complex and some mechanism can improve performance in stress situations [1]. More research is needed to determine if such adaptive mechanisms prevent stress to have a negative effect on performance. Second, the situation may also contain elements of a challenge. The concept of challenge-hindrance stressors proposes that challenge stressors have a positive motivational quality and thus, no or even positive effects on performance [67]. On the other hand, it can be associated with stress-related symptoms such as reduced well-being and impaired health [14,67,68]. Third, mostly self-reported but not biological stress is associated with poorer performance [6-8,44,45]. Biological measures may be unrelated to performance or be confounded by physical activity during CPR. Furthermore, biological measures may not differentiate between stressful and challenging situations, e.g. tense and energetic arousal. These considerations need further investigation.

8.2. Limitations and future research

This review has also shown several limitations. First even though it is evident that CPR leads to stress and performance impairments [6-8], studies mostly focus on residents [30-35] or medical students [6,7,25,44] and only two studies included more experienced personnel [29,36]. Thus, it remains empirically open to what extent such problems also persist for more experienced resuscitators.

Second, many of the research findings on the acute stress response during resuscitation are based on simulation studies, therefore, these findings cannot be generalized for real-life settings. Further, no interventions assess long-term follow-ups of CPR performance to assess the quality of the intervention or use critical outcome parameters such as survival to discharge or neurological outcome. Therefore, future studies should target real-life CPR scenarios and assess long-term parameters to be able to make valid statements concerning the effect on CPR outcome.

Third, interventions that target stress-reduction for resuscitation teams are sparse, even though many general stress-reducing interventions exist [5,57,58]. Due to the presented findings, this lack of interventions misses out on the opportunity to significantly improve resuscitation performance. Therefore, concentrating on developing such stress-reducing interventions seems worthwhile and may yield promising results for the future.

Last, this narrative review has shown a broad range of research, however, systematic reviews may be used to provide an estimate of a potential bias in published studies in this field.

9. Conclusion

In this narrative review, stress has repeatedly been shown to be increased during CPR. Even though acute stress may also show protective factors for performance, it has oftentimes been found to be associated with lower CPR performance in simulation studies. Future studies should concentrate on stress reducing interventions and team-related factors in acute CPR settings as a possibility to enhance performance during resuscitation.

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Declaration of competing interest

None declared.

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Appendix F

Study VI

Vincent, A.*, Urben, T.*, Becker, C., Beck, K., Daetwyler, C., Wilde, M., Gaab, J., Langewitz, W., & Hunziker, S. (2022). Breaking bad news: A randomized controlled trial to test a novel interactive course for medical students using blended learning. *Patient Education and Counseling, 105*(1), 105–113. https://doi.org/10.1016/j.pec.2021.05.002

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Breaking bad news: A randomized controlled trial to test a novel interactive course for medical students using blended learning

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ABSTRACT

Objective: Breaking bad news (BBN) is challenging for physicians and patients and specific communication strategies aim to improve these situations. This study evaluates whether an E-learning assignment could improve medical students' accurate recognition of BBN communication techniques.
Methods: This randomized controlled trial was conducted at the University of Basel. After a lecture on BBN, 4th year medical students were randomized to an intervention receiving an E-learning assignment on BBN or to a control group. Both groups then worked on an examination video and identified previously taught BBN elements shown in a physician-patient interaction. The number of correctly, misclassified and incorrectly identified BBN communication elements as well as missed opportunities were assessed in the examination video.
Results: We included 160 medical students (55% female). The number of correctly identified BBN elements did not differ between control and intervention group (mean [SD] 3.51 [2.50] versus 3.72 [2.34], p = 0.58). However, the mean number of inappropriate BBN elements was significantly lower in the intervention than in the control group (2.33 [2.57] versus 3.33 [3.39], p = 0.037).
Conclusions: Use of an E-learning tool reduced inappropriate annotations regarding BBN communication techniques.
Practice implications: This E-learning might help to further advance communication skills in medical students.

1. Introduction

In the moment physicians break bad news, patients come to realize that their life has just changed fundamentally and, oftentimes, challenges what patients had expected for their future. To convey news with such a high impact upon a patient's situation represents one of the most challenging communicative situations for physicians [1,2]. Therefore, breaking bad news (BBN) should be taught to medical students and considered an important element of medical curricula. Accordingly, in many countries it is an integral part of formal medical exams, and recent studies have shown that training the ability to convey bad news in a professional manner yields positive results [3,4].

When bad news are communicated poorly this may result in patient distress or confusion [5,6]. Contrarily, if it is communicated in an effective and supportive manner, patients are more likely to understand, accept and adjust to the situation [7]. For example, a truth-telling protocol had positive long-term effects on cancer patient's stress, anxiety, and depression levels [8]. Also, patient-centered communication strategies in BBN have been shown to be associated with lower psychological burden in patients and relatives [9–11]. Whereas interventions in BBN in cancer care gave equivocal results [3,12,13], intensive care research has shown that proactive communication can help to reduce negative sequelae of bad news in relatives such as depression, anxiety, complicated grief or post-traumatic stress disorder [10,11,14–16]. Even though this stresses the

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BAD
Break bad news
Do I have all the necessary information? (e.g., medical results, circumstances under which the patient was brought to hospital)
What kind of information does the patient already have (e.g., already informed about diagnoses? Does the patient know the purpose of the conversation?)
Announcement of bad news with a "warning shot" (e.g., "I am afraid, I do not have good news for you…" or "I am sorry, but I have to inform you…")
KISS - Keep it short and simple ("we have found malignant cells in your biopsy, which means that you have cancer"; "your father has died ")
Acknowledge the reaction
Wait (at least three seconds; maintain eye contact)
Address patient's emotions (NURSE)
Avoid premature reassurance (e.g., "everything is going to be okay")
Respond to patient's questions
Discuss the near future
Give information that the patient requires now
What are the concrete next steps?
Amend bad news with good news (if possible)
Make follow-up appointment

Fig. 1. BAD communication strategy for the disclosure of bad news [47]**.** Legend: NURSE, communication strategy for addressing patients' emotions with naming, understanding, respecting, supporting and exploring.

need for adequate response to patients' or relatives' emotions, emotional opportunities in BBN conversations are still often missed [17].

Therefore, different techniques have been developed to optimize communication in these situations, such as the SPIKES model [18], the ABCDE model [19] or the BAD scheme [20]. These techniques revolve around patient-centered communication, which provides not only medical information but also emotional support [21]. It involves the patient more strongly in the decision-making process [22] and consultation by exploring the patient's concerns, and assessing and responding to the patient's medical concepts [21,23]. It is associated with improved patient satisfaction, biomedical and functional outcomes [24]. One of these BBN techniques, the BAD scheme, is an acronym which stands for "Break bad news", "Acknowledge the reaction" and "Discuss the near future" [20,25,26] (Fig. 1). First, the message should be delivered by making sure to have all necessary information available, announcing the bad news by a warning shot to allow the patient to prepare for the following information, and delivering the diagnosis in a clear and simple manner following the *Keep it short and simple* (KISS) principle. Second, the physician should offer enough time for the patient to process the bad news and acknowledge the patient's reactions by offering more information when requested or responding to emotions if the patient shows signs of psychological distress. Last, the next steps should be communicated clearly and a follow-up meeting should be scheduled [20].

Successfully teaching professional communication requires different modalities. Previous studies assessing communication skills training have found that training may be most effective if provided often and early on, as in longitudinal programs [27–29]. Further, medical curricula are encouraged to include a multitude of possibilities of practicing communication strategies for effective BBN with different learning opportunities, such as lectures, role-playing, and teachable moments in clinical settings [27,29]. Learning professional behavior – as opposed to acquiring factual knowledge – depends mostly on the observation of others, such as peers or seniors who serve as role models [30–33]. Following Bandura's Social Learning Theory, observation of others and perceiving their behavior as relevant and helpful stimulates the observer to simulate the observed behavior [34]. This is especially true when learning doctor-patient communication in early stages of the medical curriculum [35]**.**

Yet it is important that the observer notices the exact elements of professional behavior to achieve an immediate learning effect [36,37]. Especially in teaching of BBN skills, observation of actual behaviors with students having multiple opportunities for demonstration, reflection, practice, and feedback are of benefit [29]. This may be achievable through blended learning, a continuously advancing innovative approach in education combining different teaching and learning formats. This gives the opportunity of combining theory and learning from role models for instance via video-based E-learning. Recently, such E-learning tools have shown promising results in different fields of medical education, such as in human anatomy [38] or the provision of clinical knowledge in urology [39]. Further, students report high acceptance towards blended learning [39,40]. Also, a pilot study in teaching BBN via E-learning showed significant improvements of medical interns' performance [4], while others have found improvements in knowledge and comfort levels of BBN [41]. Yet, no blended learning combining E-learning with regular curricular activities concerning BBN has been evaluated.

The aim of this study was to evaluate a novel interactive course for medical students using blended learning, with a lecture and a video-based E-learning tool helping medical students to identify adequate communication skills in BBN within a randomized controlled trial. The video-based E-learning is used to teach communication skills acquired by observing, recognizing, tagging and naming specific communication elements via video. The BAD scheme was chosen as the BBN communication technique as it is taught in the regular course curriculum at the medical faculty of the University of Basel and teaches three relevant goals: give bad news, listen to the response, and plan the near future. First, we specifically hypothesized that students' ability to correctly identify communication elements according to the BAD scheme would be higher in the intervention group than in the control group. Second, we

hypothesized that the amount of falsely identified communication elements will be higher in the control group than in the intervention group. Third, we hypothesized that after the teaching videos, students in the intervention group would feel better prepared for the examination video and that they would rate their own performance in the E-learning assessment higher than the control group. Further, as previous research has shown gender differences in learning styles [42], we investigated possible gender differences in our sample. Also, we aimed to explore the students' perception of the physician in the E-learning videos.

2. Methods

2.1. Study sample

In December 2019, 186 4th year medical students at the University of Basel were asked to participate in the study, of which 181 gave their informed consent. In this randomized controlled trial, a stratified randomization was used in which students were randomized 1:1 to either a control or an intervention group by a computer-generated random number list using a gender stratification to the two groups to generate an equal gender distribution. All data were anonymously extracted and all identifying data such as name, date of birth or email address were irreversibly deleted to guarantee anonymous analysis. The study was approved by the local Ethics Committee (Ethics Committee Northwest/Central Switzerland; Req-2019-01064).

2.2. E-learning tool

Medical students participated in an E-learning tool consisting of two parts. The first part includes three teaching videos demonstrating the same physician and patient during a consultation in which the diagnosis of an advanced small-cell lung cancer is communicated in an acted-out BBN situation. The physician in the videos was played by a trained male physician and the patient by a trained female actor. These videos follow the basic differentiation suggested by Brewin: An emotion-focused version, an information-focused version and finally a patient-centered version in which a combination between these two approaches following the BAD scheme is sought [43]. Further, these videos are enriched with annotations pointing to explicit communication elements demonstrated by the physician. Annotations were presented as pop-ups next to the video commenting on a certain communication strategy at the exact time as displayed in the video, ensuring that students noted the communication elements displayed. Students were able to replay the videos and read the annotated comments as often as needed. The duration of the teaching videos were around 4 min each. Both training and examination videos were set in a physician's office and actors received systematic training on the role and medical background information.

Then, an examination video with a BBN situation was shown in which students were asked to make their own annotations, i.e. recognize, tag and name specific communication elements according to the BAD scheme. In this video, the physician was played by a trained female physician and the patient by a trained female actor. Further, students were asked to identify missed opportunities to use BAD communication elements. The duration of the examination video was 4 min. Students had a fixed timespan of 20 min to watch and annotate the examination video, as monitoring of the students at home was not possible. Medical students at the University of Basel are used to identifying communication techniques in prototypical physician-patient consultations, i.e. explicit demonstration of communication strategies, from previous assignments. Therefore, the examination video in this study did not show a prototypical but an ordinary bad news situation, i.e. no explicit use of a structured communication strategy and combining professional and inadequate communication elements, because everyday role-models rarely behave like communication experts [44]. The examination video shows a senior consultant informing a 40-year-old female patient that her hip prosthesis should be removed due to a chronic infection.

2.3. Implementation of educational intervention

All medical students attended a mandatory lecture teaching BBN focusing on the BAD scheme [20,45]. This lecture is an integral part of the longitudinal communication curriculum at the University of Basel in the 1st Master term. All students received the lecture on communication skills in BBN on December 3rd, 2019.

After the lecture, students gave informed consent to participate in the study and were randomized to two groups. Thereafter, students participated in the E-learning tool consisting of teaching videos and an examination video. The intervention group first worked on the teaching videos directly after the lecture which were released for 1 week (4.12.–11.12.2019) and was then able to access the examination video (12.12.–15.12.19). To assess the effectiveness of the E-learning tool, students randomized to the control group annotated the examination video at the same timepoint as the intervention group with the knowledge of the lecture but without previously watching the teaching videos. To offer students the same amount of teaching, the control group gained access to the teaching videos after completion of the examination video (16.12.–20.12.19). At the end of the teaching and examination videos, students were asked to complete a short questionnaire to assess endpoints and predictors.

2.4. Measures

Two of the authors (A.V. and T.U.) independently rated annotations of all students given in the examination video. Raters were blinded concerning group allocation of the student annotations. In order to enable categorization of the different elements occurring in the BBN conversation, a template following the BAD scheme was used [46,47] (Fig. 1). The examination video did not show a prototypical BBN communication, but also included communication elements that could be viewed critically. Therefore, the template incorporated two dimensions: The first listed communication elements that were present in the physician's attempt to BBN, with a maximum of 21 communication elements potentially being rated. The second referred to missed opportunities in which the physician could have exhibited a more suitable communication behavior according to the BAD scheme, with 14 opportunities as a maximum. The four categories that could be rated according to the template are shown in Fig. 2. Unclear ratings and disagreements were resolved with a third author (W.L.). Interrater reliability between the two raters A.V. and T.U. was 77.7%.

Therefore, the primary outcome is the accuracy in students' ability to identify physician utterances that concur with elements of professional communication of bad news. Accuracy is defined as the amount of correctly identified professional utterances (e. g. giving a warning, attentive listening) and the amount of correctly identified missed opportunities (e.g. lack of responding to patient emotion).

Secondary outcomes were defined as inaccuracy, e.g. the amount of wrongly identified elements of professional communication, either as misclassifications (e.g. misclassifying a "respecting" as an "understanding") or incorrect identifications (e.g. items that are not associated with the BAD scheme).

Further secondary outcomes were number of identifications of BAD elements overall, perceived preparedness for the examination video rated on a visual analog scale (VAS) 0–100, and perceived self-rating of own performances in this E-learning assessment on a VAS 0–100.

Category	Explanation and example
Correct identification of BAD elements	A communication strategy is described which the physician applies in the conversation. *"The physician pauses" "Keep it short and simple"*
Correct identification of missed opportunity for BAD elements	A communication strategy is described, which the physician failed to apply. *"NURSE was not applied; the physician shows no understanding for the reaction of the patient."*
Misclassification of BAD elements	A communication strategy is wrongly identified. *"The physician applies the strategy "Respecting" [however, the strategy is "Understanding"]."*
Incorrect identification of BAD elements	Items that are not associated with the BAD scheme. *"It is important to ask about the circumstances at home."*

Fig. 2. Rating categories of students' identification of communication elements according to the BAD scheme.

Further, student- and video-associated predictors were assessed. Student-related factors were socio-demographics, e.g., age, gender, nationality, as well as personal experience with a BBN situation (e.g., as a family member) and were assessed after the examination video. After each teaching video, video-associated predictors were assessed such as perceived competence, empathy, comprehensibility, and trustworthiness of physician.

2.5. Data analysis

To characterize the study population, descriptive statistics including means (M) and standard deviations (SD) were used for continuous variables as appropriate. Frequencies were used for binary or categorical variables. The primary outcome variable was tested for normality with visual inspection of the Q-Q plot. We used *t*-tests to calculate differences and estimated Cohen's d for effect size between the intervention and the control group for the primary and secondary outcomes, as well as for gender differences. Further, we calculated 2 × 2 ANOVAs for group and gender differences to calculate possible interaction terms. Last, we calculated univariable regression models for video-associated predictors with the three teaching videos. STATA 15.0 was used for all statistical analyses and a two-sided p-value of <0.05 was considered significant.

3. Results

3.1. Demographics

Of 186 potentially eligible 4th year medical students, two students did not give informed consent, three students did not visit the lecture, 4 students did not complete the examination video and 17 were lost due to technical problems. A total of 160 students annotated the examination video, of which 80 students were in the intervention group (56% female) and 80 in the control group (54% female). Table 1 shows the characteristics of student population overall and stratified by intervention and control group. There were no significant differences between the intervention and control group regarding their baseline demographics. Interestingly, 42.1% of the students had already experienced a BBN situation, with no difference between groups.

3.2. Intervention

No significant differences were found between the intervention and control group regarding correct identification of BAD elements, the number of identifications of BAD elements overall, correct identification of missed opportunities, or misclassification of BAD elements (Table 2a). However, the number of incorrectly identified elements was significantly higher in the control group versus in the intervention group (M [SD] 3.33 [3.39] versus 2.33 [2.57], p = 0.04, d = 0.33). Further, there were no significant differences between the intervention and control group regarding the self-ratings of preparedness for examination and performance in the examination video.

Table 2b shows the mean number of the identified communication elements stratified by gender. The mean number of all annotated items was significantly higher in women than in men (M [SD] 11.32 [6.05] versus 9.43 [5.39], p = 0.04, d = 0.33). Also, correctly identified BAD elements and correctly identified missed opportunities were rated significantly more often by female than male students. No significant differences were found in misclassified or incorrectly identified items. Further, no significant interactions between group and gender for the primary and secondary outcomes were found.

3.3. Video-associated factors

155 students (75 in the intervention and 80 in the control group) rated the perceived competence, empathy, comprehensibility, and trustworthiness of the physician in the three different E-learning teaching videos (patient-, emotion- and information-centered) Table 3 and Fig. 3. The doctor in the patient-centered video was perceived as more competent than in the emotion-centered (Coeff −8.34, 95%CI −12.37 to −4.31, p < 0.001) and in the information-centered video (Coeff −11.58, 95%CI −15.61 to −7.55, p < 0.001). The information-centered video was perceived as significantly less empathic (Coeff −20.8, 95%CI −25.37 to −16.23, p < 0.001) and comprehensible (Coeff −16.71, 95%CI −21.09 to −12.33, p < 0.001) than the patient-centered video. The patient-centered video was perceived as significantly more trustworthy than the emotion-centered (Coeff −8.47, 95%CI −13.62 to −3.33, p = 0.001) and the

Table 1
Demographic characteristics of student population overall and stratified by group.

Variable		All	Intervention group	Control group	p
N		160	80	80	
Age (years), mean (SD)		22.8 (4.2)	22.4 (4.7)	23.2 (3.6)	0.20
Female gender, n (%)		88 (55.0%)	45 (56%)	43 (54%)	0.75
Nationality, n (%)	Switzerland	133 (83.6%)	69 (87%)	64 (80%)	0.30
	Swiss dual citizen	16 (10.1%)	8 (10%)	8 (10%)	
	Germany, Austria, Liechtenstein	6 (3.8%)	1 (1%)	5 (6%)	
	Other European country	2 (1.3%)	0 (0%)	2 (3%)	
	Other	2 (1.3%)	1 (1%)	1 (1%)	
Past experience with BBN situation, n (%)		67 (42.1%)	30 (38%)	37 (46%)	0.29

Legend: n, number; SD, standard deviation; BBN, breaking bad news.

information-centered video (Coeff −21.75, 95%CI −26.89 to −16.6, $p < 0.001$).

4. Discussion and conclusion

4.1. Discussion

The main findings of this randomized controlled trial assessing whether a novel blended E-learning could enhance the identification of adequate communication skills in a BBN situation of medical students are threefold. First, intervention group students who watched the teaching videos before the examination video were significantly less prone to incorrectly identifying elements of communicating bad news. Second, independent of our intervention, we found gender differences with female students showing better results compared to male students. Third, the physician in the patient-centered video was perceived as more competent, empathic, comprehensible, and trustworthy than in the other two videos, showing that students were able to differentiate between different modes of delivering bad news.

The finding that students were less prone to incorrectly identifying elements of communicating bad news is important. BBN communication strategies are very specific about which points to address in a BBN situation and, more importantly, about giving the patients enough time to process the situation through attentive listening, and only offering more information if requested [18,20]. This is partly because during stressful or emotional situations, attentional narrowing occurs, in which only the very central message is exclusively focused on, disregarding peripheral information [48,49]. Since patients' capacity to remember medical information is generally limited [49–51] and certain communication skills like explicitly structuring information help to increase the information recall [52], only the very essential information should be given in a BBN situation. Therefore, the finding that the intervention group annotates less inappropriate BAD items is important, since it shows that the intervention group not only knows what to say – but more importantly what not to say. Few other studies have evaluated the impact of E-learning interventions on the improvement of communication in BBN situations. Two studies found that communication was improved through E-learning tools concerning student knowledge and comfort levels [41] and the use of proper communication skills [4]. Another study found an E-learning trial in BBN using hints in a preparatory task to have beneficial effects on medical students' performances later on [53], which resembles the annotations in our E-learning module. Further, E-learning interventions have been found to be non-inferior to lectures [54]. In our study, all students had received a lecture on the BAD scheme before the E-learning intervention, therefore, the effect of the lecture alone cannot be assessed in our study design.

The few resulting differences between the intervention and the control group may be explained by the high training standards of the student sample. Students at the University of Basel receive a longitudinal training in professional communication with lectures, practice with simulated and real patients as well as E-learning tools [55]. BBN is not a completely new set of communication techniques but a combination of elements that students already know: using the book metaphor [52], pausing after conveying complex information [46] and responding to emotions with the NURSE model [44,46]. Therefore, results may have been akin to a ceiling effect. Also, we used an examination video showing an ordinary communication example of a clinician, i.e., demonstrating professional as well as inadequate communication elements, yet the learning videos showed prototypical BBN situations. Shifting from prototypical to ordinary situations could enhance learning but also the exercise's difficulty, since non-prototypical examples demand more from students as it is presented less clearly, with more digression and without explicit structuring. Yet, it also poses a potential lack of comparability between the videos since it makes detection of differences more difficult. A possibility to improve our E-learning could be the use of more erroneous teaching videos as a previous trial showed that erroneous video-based examples foster better communication skills [56]. Still, the E-learning significantly minimized the number of inappropriate annotations unrelated to the BAD scheme, therefore, communication techniques that are especially relevant for BBN might be identified more precisely by using the E-learning.

We found significant gender differences in our analysis in favor of female students, as women identified more elements overall, and correctly identified more BAD elements and missed opportunities. However, there were no gender differences regarding misclassified or incorrectly identified items. This might be due to learning styles,

Table 2a
Students' performance in identifying communication elements according to the BAD scheme overall and stratified by group.

Variable	All	Intervention group	Control group	p	*Cohen's d*
N	160	80	80		
Identification of BAD elements overall, mean (SD)	10.47 (5.82)	9.84 (5.44)	11.10 (6.15)	0.17	0.22
Correct identification of BAD elements, mean (SD)	3.62 (2.42)	3.51 (2.50)	3.72 (2.34)	0.58	0.09
Correct identification of missed opportunity for BAD elements, mean (SD)	2.37 (1.65)	2.49 (1.59)	2.25 (1.70)	0.36	0.15
Misclassification of BAD elements (mean, SD)	1.55 (1.49)	1.41 (1.40)	1.69 (1.57)	0.24	0.19
Incorrect identification of BAD elements, mean (SD)	2.83 (3.04)	2.33 (2.57)	3.33 (3.39)	**0.04**	**0.33**
Self-perceived preparedness for examination, mean (SD)	53.40 (22.26)	56.71 (20.08)	50.09 (23.91)	0.06	0.30
Self-rating performance, mean (SD)	51.24 (21.56)	52.60 (20.21)	49.88 (22.88)	0.43	0.13

Legend: n, number; SD, standard deviation; BAD elements, elements according to BAD communication strategy.

Table 2b
Students' performance in identifying communication elements according to the BAD scheme overall and stratified by gender.

Variable	All	Female	Male	p	*Cohen's d*
N	160	88	72		
Identification of BAD elements overall, mean (SD)	10.47 (5.82)	11.32 (6.05)	9.43 (5.39)	**0.04**	**0.33**
Correct identification of BAD elements, mean (SD)	3.62 (2.42)	4.16 (2.46)	2.96 (2.20)	**<0.01**	**0.51**
Correct identification of missed opportunity for BAD elements, mean (SD)	2.37 (1.65)	2.60 (1.77)	2.08 (1.44)	**<0.05**	**0.32**
Misclassification of BAD elements, mean (SD)	1.55 (1.49)	1.58 (1.41)	1.51 (1.59)	0.78	0.05
Incorrect identification of BAD elements, mean (SD)	2.83 (3.04)	2.85 (3.18)	2.79 (2.89)	0.90	0.02
Preparedness for examination, mean (SD)	53.40 (22.26)	51.73 (22.80)	55.44 (21.57)	0.29	0.17
Self-rating performance, mean (SD)	51.24 (21.56)	48.77 (21.77)	54.25 (21.07)	0.11	0.26

Legend: n, number; SD, standard deviation; BAD elements, elements according to BAD communication strategy.

Table 3
Univariable associations of the patient-, emotion- and information-centered E-learning teaching videos with physician-related factors (competence, empathy, comprehensibility, trustworthiness).

	Competence		Empathy		Comprehensibility		Trustworthiness	
Video	Coefficient (95%CI)	p	Coefficient (95%CI)	p	Coefficient (95%CI)	p	Coefficient (95%CI)	p
Patient-centered	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Emotion-centered	-8.34 (−12.37, −4.31)	**<0.001**	2.19 (−2.38, 6.77)	0.35	-0.59 (−4.97, 3.79)	0.79	-8.47 (−13.62, −3.33)	**0.001**
Information-centered	-11.58 (−15.61, −7.55)	**<0.001**	-20.8 (−25.37, −16.23)	**<0.001**	-16.71 (−21.09, −12.33)	**<0.001**	-21.75 (−26.89, −16.6)	**<0.001**

Legend: CI, confidence interval.

as female physicians have been found to perform more standardized examinations and adhere higher with evidence-based guideline recommendations compared to male physicians [42]. Yet, other studies reported that female students conduct more patient-centered interviews than male students in BBN scenarios [57] and female physicians provide more patient-centered care [58]. While identifying BAD strategies cannot be directly linked to patient-centeredness, BAD strategies are tools for patient-centered communication and our results show female students identifying more such patient-centered elements overall. However, other findings showed that patient-centered communication is not related to gender in hospital consultants when BBN [59]. Thus, in conclusion, the results indicate the need for more individualized, gender-specific training in patient-centered communication in BBN situations, at least for inexperienced physicians and medical students.

Interestingly, the perception of the different communication styles shown in the three E-learning videos differed between the videos. Most importantly, the patient-centered version following the BAD scheme was rated as favorable by the students. This is in line with other research showing that patient-centered communication in BBN situations was perceived as the most emotional, least dominant, and most appropriate when conveying information [26]. Further, patient-centered communication showed highest satisfaction and least increase in negative emotions, and may have the most positive outcome for recipients of bad news on cognitive, evaluative, and emotional levels [26]. Importantly, these results confirm that the videos displayed the intended effects of certain communication tools and that the patient-centered version is seen as favorable by students, endorsing the validity of the E-learning.

This trial has several limitations. First, student annotations as a test for communication skills might limit the generalizability on the future physician-patient interactions of students. While the application of the BAD scheme was possible through web annotations, a test in a face-to-face BBN situation measuring students' behavior change could be helpful in testing the external validity of the trial. Second, a further limitation poses the loss of data due to technical reasons. Some students reported breaking off the online session too early which resulted in their answers not being saved. For those students, we could reset the program to allow them a second chance, yet, we assume that 17 students did not turn to our technical support for this matter or did not realize that they prematurely left the online session, therefore, resulting in this loss of information. Third, since the examination video showed an ordinary situation, yet the learning videos were based on prototypical situations, the

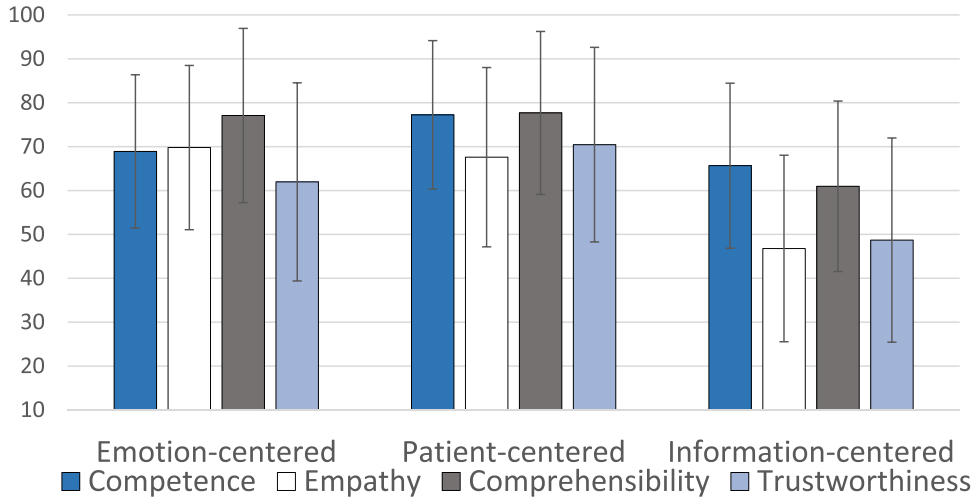


Fig. 3. Perception of physician-related factors for the three E-learning teaching videos.

comparability between the videos is difficult. As aforementioned, an examination video which demonstrates a similarly prototypical situation, or the use of more erroneous video-based examples for the learning videos [56], may be needed to clarify this matter. Yet, the fact that the E-learning did not involve face-to-face communication should not have made an impact on the quality of learning, as a previous study demonstrated no difference between active and passive learners' skills in BBN [57]. Last, only a low percentage of possible communication elements were detected by the students. However, this was not surprising due to the aforementioned complexity of the task and the time restriction given during the examination video.

4.2. Conclusion

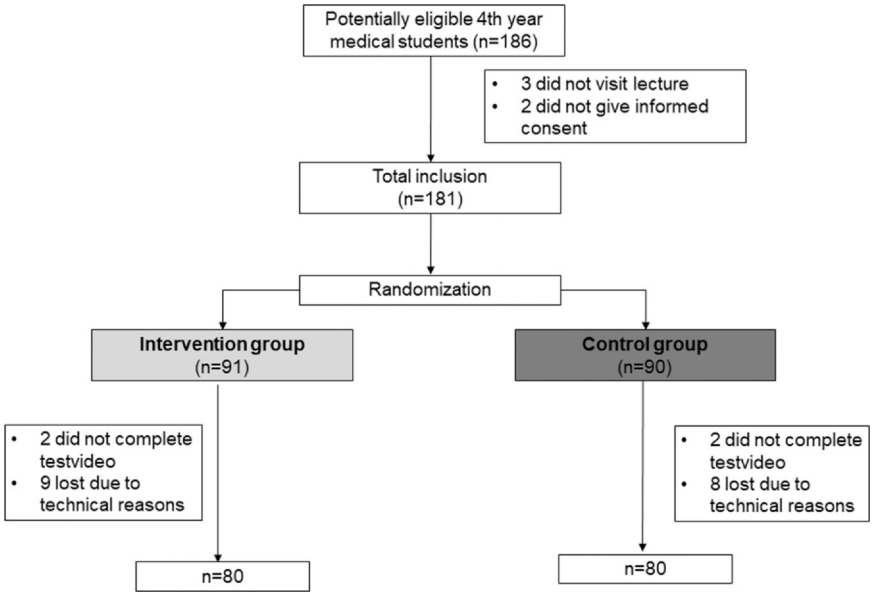
In conclusion, the use of an E-learning tool reduced incorrect identifications regarding the BAD communication technique and might help to further advance communication training in medical students embedded in a longitudinal curriculum. Further, the intended differences in the three E-learning videos were correctly identified by the students. As blended learning becomes an increasingly important education tool, it is worthwhile to further investigate the best-possible design for a broad implementation in medical curricula.

4.3. Practice implications

This E-learning may help to further advance communication training in medical students in an easily accessible, low-threshold manner. Further, especially the found gender differences should be considered in future online tools to assure the best possible conveyance of communication techniques.

Appendix

See appendix E-Fig. 1.



E-Fig. 1. Study flow of the students included in the trial.

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CRediT authorship contribution statement

Alessia Vincent: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft. **Tabita Urben:** Data curation, Formal analysis, Investigation, Project administration, Writing - original draft. **Christoph Becker:** Conceptualization, Validation, Writing - review & editing. **Katharina Beck:** Conceptualization, Validation, Writing - review & editing. **Christof Daetwyler:** Conceptualization, Data curation, Validation, Project administration, Resources, Software, Writing - review & editing. **Michael Wilde:** Conceptualization, Data curation, Project administration, Resources, Writing - review & editing. **Jens Gaab:** Validation, Writing - review & editing. **Wolf Langewitz:** Conceptualization, Funding acquisition, Resources, Supervision, Validation, Writing - review & editing. **Sabina Hunziker:** Conceptualization, Funding acquisition, Resources, Supervision, Validation, Writing - review & editing.

Declarations of competing interest

None.

Informed consent and patient details

I confirm all patient/personal identifiers have been removed or disguised so the patient/person(s) described are not identifiable and cannot be identified through the details of the story.

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