# Evaluation of hospital outcomes

# Predictors of length of stay, rehospitalization and mortality

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# CHAPTER I

## Introduction

## 1. Background

One of the leading challenges in public health is to provide optimal care while effectively managing costs. A major health issue concerning cost effectiveness is the aging population and the increasing prevalence of chronic comorbidities and multimorbidity. Although healthcare cost are increasing rapidly, health care system spending is not necessarily correlated with favorable patient health outcomes. [1] Public hospitals play a key role in the delivery of health care of the population. However, they are often confronted with the pressure to improve quality standards while maintaining or even reducing costs. Moreover as reported by Tynkkynen and Vrangbæk in a scoping review of hospital services in Europe: "Public hospitals tend to treat patients who are slightly older and have lower socioeconomic status, riskier lifestyles and higher levels of co-morbidity and complications than patients treated in private hospitals." [2]

In order to monitor and compare hospital performance, outcome measures for quality of care have been developed and progressively employed. [3] Three main important outcome measures that are commonly used as quality indicators are length of hospital stay, rehospitalization and mortality rate. [3]

### 1.1. Length of hospital stay.

Length of hospital stay (LOHS) refers to the duration of a patient's hospitalization from admission to discharge. The most commonly used operational definition of LOHS is based on the calculation of the date of discharge minus the date of admission (Organisation for Economic Cooperation and Development, 2014). There is substantial variation between hospitals and among countries in the mean LOHS, however in 2018, the average length of stay in hospitals for all causes of hospitalization was 7.5 days across EU countries. (Figure 1) LOHS is a critical factor in the strategic planning and allocation of hospital resources and it is often used as a quality indicator of the efficiency of hospital management. [4–8] Literature has shown that a reduction of LOHS is associated with a decreased risk of infection and medication side effects. [9,10] Moreover, a decrease in the number of inpatient days resulted in improved quality of treatment and increased hospital profit with more efficient bed management. [11] Thus, insight into the factors associated with LOHS is essential to improve hospital care and maintain or reduce costs.
Switzerland has one of the highest health care spending per capita worldwide; in fact the Organisation for Economic Co-operation and Development (OECD) estimated that in 2019 the health spending reached 11.3% of the gross domestic product (GDP) compared to a OECD average of 8.8%. [12] In order to address

the constant increase in cost and the risk of overtreatment, in 2008 the Swiss parliament decided to adopt a prospective hospital payment method based on diagnosis-related groups (DRGs) changing from a fee-for-service per diem system. The introduction of the new system was completed in all regions of Switzerland by the 1st of January 2012. The scope of the DRGs payment system was to reduce health expenses, raise management efficiency and diminish the financial incentive to fee-for-service hospitals for keeping patients longer than necessary. [13,14]

With this new payment method, hospitals are reimbursed based on each DRG, regardless of the actual workload of the specific case. As consequence, hospitals have to optimize treatment processes to be cost-neutral. Research studies on Swiss DRGs showed that the average LOHS of patients has decreased since its implementation [11,15]. However, it has to be taken into consideration, that hospitals might have a negative incentive to discharge patients prematurely, which may leads to adverse health outcomes. [11,16,17]

Moreover, despite an overall decline in the LOHS on a national level, public hospitals also treat patients, the so-called high outliers, with above-average LOHS who fall outside the norm according to Swiss DRG. Therefore, it is fundamental to find new strategies that allow predicting LOHS more accurately.

A recommended approach to timely discharge, which is important for both the patient and the healthcare service, is to initiate discharge planning early in the admission process, rather than waiting for medical issues to be resolved [18]. Hence, prediction models based on factors that are available at time of hospital admission or at least within the first days are highly needed to optimize the process of discharge management.

**Predictors of length of hospital stay.**

Buttigieg and colleagues [19] conducted an extensive literature review with the aim of identifying factors associated with the LOHS and categorize them in four main groups:

*I. Healthcare system factors*
*II. Patients characteristics*
*III. Processes*
*IV. Outcome indicators*

*I. Health care systems' factors*

The characteristics of health care systems, such as *access and admitting services*, availability of beds, clinical pathways, and transferring to rehabilitation or long-term care facilities, can influence the patient's LOHS. Access and admitting services include information such as method of admission, (whether emergency or elective) and date and time of admissions. Literature showed that patients admitted over weekends, holidays, or during afternoons and outside office hours tend to have increased LOHS. Delays in performing procedures on weekends can also lead to greater mortality and longer LOHS. [20–24]

I*nsufficient bed capacity* or bed-blocking can result in congestion in the ED and prolonged LOHS. Outlying patients in other wards may receive lower standards of care and experience increased LOHS and readmission rates.

*Clinical pathways*, which define the sequence and timing of health interventions, can minimize resource utilization, and enhance quality of care. Those pathways have been found effective for invasive procedures but may have varying effects on the LOHS, depending on the condition being treated.

The efficiency and availability of allied professionals and *support services*, such as laboratories and radiology departments, are crucial for timely and efficient interventions. Adequate availability of allied health professionals and timely imaging can lead to shorter LOHS.

Transfer between facilities: Balancing admissions and discharges is important within hospitals. Early admission to specialized centers, such as rehabilitation programs, can reduce LOHS and improve patient outcomes.

*II. Patient characteristics*

Patient characteristics comprehend demographic attributes and health related factors.

Philp et al. (2013) highlighted that among demographic characteristic advanced old age, low socio-economic status, lack of family support, loneliness and living in a care facility were identified as factors associated with increased LOHS. [25] Elderly patients, who make up a significant portion of hospital admissions, tend to have longer LOHS. The availability of social support is associated with better prognostic outcomes since it helps to overcome stressful life events, improves adherence to medical treatment, and enhances recovery. However, even when social support is present, it may be insufficient due to increased burden on caregivers, associated with factors such as caregiver's age, social, emotional, and financial losses, and lack of respite. Other social issues that can influence LOHS include a lack of identified caregivers, waiting for foreign domestic helpers or caregiver training, and waiting for placement in a nursing home.

Health related factors include main diagnosis at admission, disease severity, medical history, number, and type of comorbidities.

The main diagnosis at admission refers to the primary condition or reason for hospitalization. Studies have shown that certain medical conditions or diagnoses are associated with longer LOHS. For example, complex surgeries, severe infections, chronic conditions requiring extensive management, or conditions requiring specialized care such as cancer treatments may result in prolonged LOHS [26–30].

Comorbidities are secondary diagnoses and distinct from the reason for the hospitalization (i.e., the principal diagnosis). [31] The presence of additional health conditions during a hospital stay, can significantly impact patient care. Concurrent and multiple comorbidities require extra clinical assessment or treatment, nursing care and monitoring. [32,33] It is crucial to study the patterns of comorbidities associated with inpatient stays for various reasons.

As health-related factors can significantly impact the length of hospital stay. It is important for healthcare providers to consider these factors in patient care planning, resource allocation, and discharge planning to optimize the efficiency and effectiveness of healthcare delivery.

*III. Processes*

Process-related factors that influence LOHS can be summarized in six main subgroups:

Clinical caregivers' characteristics play a role because health professionals can influence the length of stay with their decisions. Variations in decision-making can occur between geographical areas, hospitals, and physicians [34].

Communication and multidisciplinary approach are also critical factors [35]. "Communication and effective team care among diverse professionals can enhance patient outcomes and decrease the LOHS". [36] However, interdisciplinary communication can pose challenges, especially when patient information are not completely and clearly handed over when various health professionals are involved." [37,38]

Comprehensive discharge planning plays a crucial role in optimizing bed utilization mitigating bed-blocking and lowering readmission rates [39]. Research has shown that early discharge planning, which includes assessing functional needs, providing education to patients and caregivers, and reviewing medications, can effectively reduce readmissions. Moreover, involving patients and their families in the discharge planning process has the potential to improve patient outcomes and satisfaction [40–42]

*IV. Outcome indicators*

Outcomes indicators associated with LOHS are primarily complications and rehospitalization. Compared to the first 3 categories described above (healthcare system factors, patient characteristics and processes), outcomes indicators can be considered rather as factors associated with LOHS instead of predictors.

As previously mentioned, prolonged LOHS is a potential risk factor for hospital-acquired complications (especially infections). Conversely, it is important to recognize that complications themselves can contribute to a prolonged LOHS. Literature has shown that patients with complications experience significantly longer hospital stays compared to those without complications, highlighting the detrimental impact of these adverse events on the duration of hospitalization. [9,10,21]

Patients who experience complications may require additional medical interventions, specialized care, or extended monitoring to address and manage these adverse events effectively. [43–45]

Therefore, LOHS and complications are factors that influence each other: while prolonged LOHS may increase the likelihood of developing complications, the occurrence of complications can subsequently contribute to an extended duration of hospitalization. This complex relationship underscores the need for healthcare providers to implement preventive measures and strategies to minimize both unnecessary prolongation of hospital stays and the occurrence of complications, ultimately improving patient outcomes and optimizing resource utilization.

The second important outcome indicator related to length of hospital stay is rehospitalization. Since rehospitalization represent also one of the quality indicators analyzed in this project, a detailed description can be found in the following sub-chapter.

## 1.2. Rehospitalization

Rehospitalization, defined as the readmission of patients to a hospital within a specified period after their initial discharge, is an important quality indicator that reflects the effectiveness of care transitions, post-discharge management, and care coordination. The high variability of readmission rate can be seen across countries, regions and centers and could partially be avoidable. [46–48]

Unplanned rehospitalizations are often associated with emotional distress for patients and their care givers, as well as increased morbidity and mortality [49]. They can lead to increased dependence on the hospital, especially in the elderly, and thus to a vicious cycle of repeated hospitalizations. [49]

The introduction of the DRGs system in Switzerland did not only impact LOHS as discussed in the previous sub-chapter (see *2.1 Length of hospital stay* p. 6-11) but also rehospitalization. When rehospitalization occurs within 18 days from discharge and with the same primary diagnosis, the two hospitalizations are merged in one. [50] This means that the hospital receives significantly less or even no reimbursement for the second hospitalization.

High rates of rehospitalization suggest gaps in continuity of care, inadequate follow-up, medication errors, or unresolved health problems. On the other hand, lower rehospitalization rates indicate successful post-discharge care and effective transitional support. Understanding the factors contributing to rehospitalization rates enables the development of targeted interventions, such as care coordination programs, discharge planning improvements, and enhanced post-discharge follow up. [51,52] Therefore, identifying patients who are particularly at risk for unplanned rehospitalization is a key step in reducing rehospitalization rates. [53]

**Predictors of rehospitalization**

In our recently published mini-review, we examined the current state of the literature on the topic of predictors for early rehospitalizations [54]. We also compared the predictors found in literature to the results of our study entitled “Predictors for unplanned readmissions within 18 days after hospital discharge: A retrospective cohort study". [55]

Similar to the LOHS, the predictors that are associated with rehospitalization can be located on different levels.

*I. Healthcare system factors*

The main system related factors associated with rehospitalization were related to the availability of primary care and the introduction of a new reimbursement system.

In the first case not being referred to the primary care physician or not having a family doctor already prior to the initial hospitalization was indicated as predictor of increased probability of readmission [56]. The availability of primary care facilities seems to be an important factor in the avoidance of unnecessary rehospitalizations and ensure the continuity of care.

In the second case, the analysis of administrative data from the Swiss Federal Statistical Office showed that there was a significant increase in the 30-day rehospitalization rate after the introduction of SwissDRGs [57].

*II. Patient characteristics*

Various patient-related predictors of early readmission were identified, in 17 studies. Similar to the predictors of LOHS, patients' characteristics can be divided into demographic and health related factors.

Also in this case, increasing age was found to be a predictor [58,59]Whereas conflicting results were found regarding patient gender: in some cases male patients were readmitted more frequently than females [58] whereas in another no differences were detected [60].

Health related factors include type and severity of the diagnosis, medical history, type of comorbidities and laboratory values.

Above all, diseases of the cardiovascular system [59–63] and neoplasms [53,59,61,64,65] were identified by numerous studies as particularly prone to readmission. Divergent results were obtained by another study, which did not find the diagnoses diabetes mellitus and malignancies to be more frequent in the group of rehospitalized patients [60]

As previously mentioned comorbidities are key indicators not only for LOHS, but also for factors such readmission rates, and mortality [53,56,58,59,62–64,66–68].

Medical history was assessed in most studies, especially in light of previous rehospitalization, that were significantly associated with higher risk of readmissions [53,56,58,59,61,64,66].

With regards to biomarkers some laboratory values deviating from the normal range were found to be significantly more frequent in patients who were readmitted, like for example in the case of hyponatremia or anemia [53,61,64].

*III. Processes*

Practitioner-related predictors.

Regarding clinical caregivers' characteristics, two studies examined the characteristics of treating physicians with respect to differences in rehospitalization rates. In terms of gender of the treating physicians, two studies reached contradictory results [69,70]. No significance was found for the number of years of experience of the physician [69]. However, a certain degree of clinical activity seems to be important, because physicians who had discharged less than 100 patients per year had higher rehospitalization rates[69].

Concerning communication, studies showed that a lack of information or communication problems, such as language barriers, were identified as factors associated with the risk of rehospitalization[71].

*IV. Outcome indicators*

Concerning the association between LOHS and rehospitalization it is interesting to mention that usually it is not linear, in fact potentially avoidable rehospitalizations occur more frequently if the observed length of stay is either significantly longer or significantly shorter than the DRG predicted length of stay.

Finally, it is also important to mention that scoring systems have been developed that can be used to identify patients who are particularly vulnerable and at risk of worse outcomes. It is however still debated if a general score (like the Hospital Score [64,72] is recommended or whether disease-specific scores should be added to the prediction models [73].

### 1.3. Mortality

Mortality is a critical outcome measure not only for clinical investigations but also in terms of health system and services research. Mortality can be assessed within a specific time frame, and it is often reported as in-hospital mortality, 30-day mortality, or one-year mortality.

Mortality rates are essential indicators for evaluating the quality and safety of healthcare interventions and practices. High mortality rates may reflect inadequate or suboptimal care, treatment complications, delayed interventions, or system failures.

In internal medicine wards in hospital mortality ranged between 3% and 13% and although it has been recognized as one of the most important indicators of quality of care, studies highlighted the need of taking into consideration also post discharge rates, mainly early post discharge (30 days) but also long term (1 year) mortality. [74–79]

This may be particularly relevant for internal medicine patients, who are increasingly burdened by multimorbidity, polypharmacy, frailty and dependency that may worsen over the course of the hospital stay and may be associated with both higher in-hospital and post-discharge mortality [80,81].

Factors that are commonly associated with LOHS and rehospitalization can also have a negative effect in terms of mortality. The following factors in particular should be emphasized: hospital-related adverse events, such as bed confinement, negative drug reactions and hospital-acquired infections. [82,83].

Concluding LOHS, rehospitalization and mortality are important quality indicators that provide valuable insights into the outcomes of care, resource utilization, and patient management. Several factors (belonging to main four areas: *healthcare system factors, patient's characteristics, processes related factors and outcome indicators)* can be associated with LOHS, rehospitalization and mortality.

## 2. Aim and relevance.

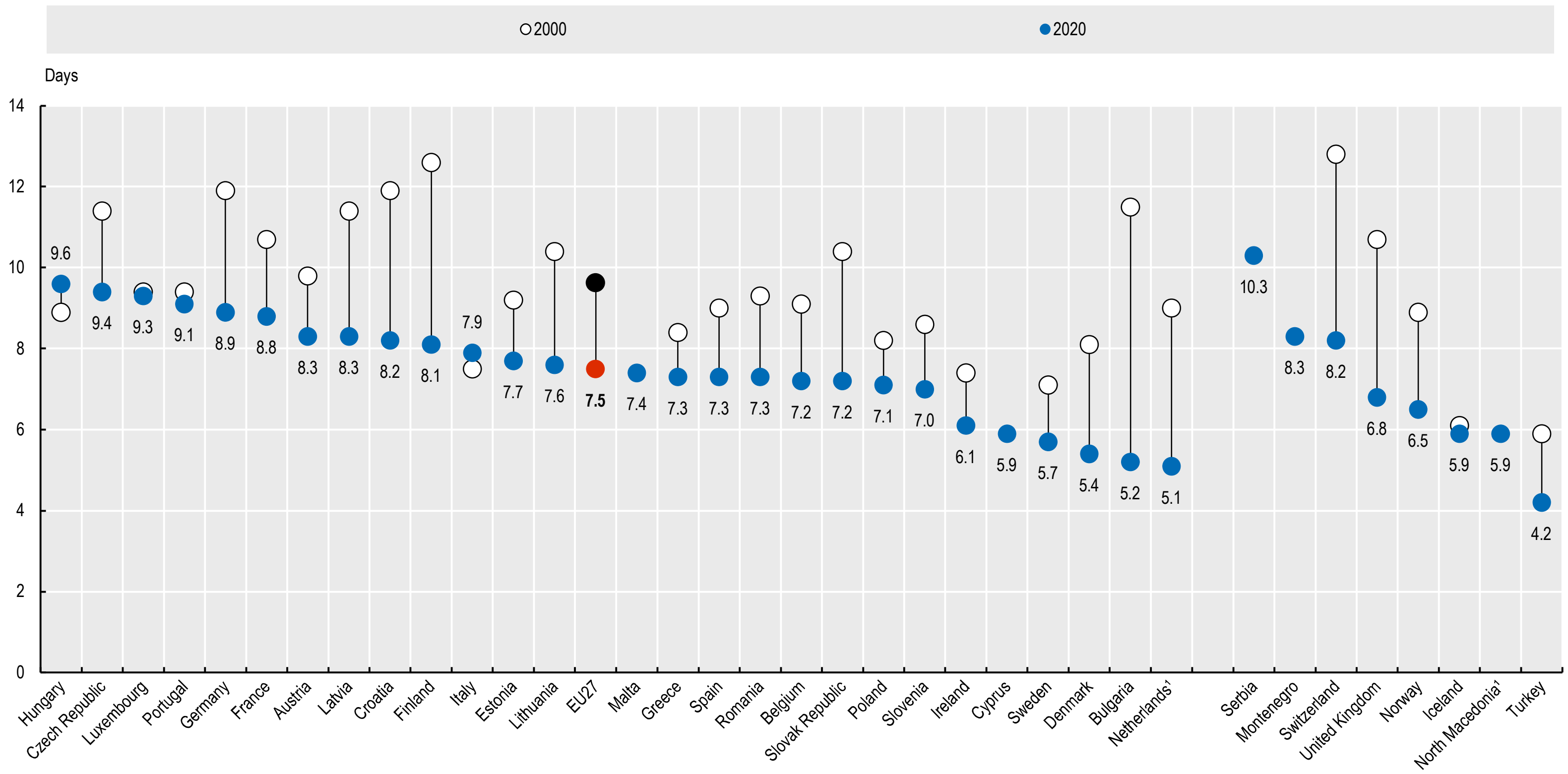
After defining and explaining the significance of LOHS, rehospitalization and mortality as quality indicators in health system and services research, it is essential to identify the factors that influence these outcomes in order to improve patient care and resource allocation. Therefore, our research focuses on identifying predictors of the three main outcomes: LOHS, mortality, and rehospitalization, in patients with specific conditions such as pulmonary embolism (PE), chronic obstructive pulmonary disease (COPD), and community-acquired pneumonia (CAP). By understanding the factors that influence these outcomes, we can address modifiable factors to develop strategies for improving patient outcomes.

In cases where predictors are non-modifiable, such as demographic or clinical characteristics, raising awareness among clinicians about the associated risk profiles becomes crucial. Additionally, these findings can inform the development of better prediction models and facilitate the adaptation of hospital bed management strategies to meet the specific needs of patients.

The aim of this thesis is to contribute to the existing knowledge by investigating and identifying predictors of LOHS, rehospitalization and mortality in patients with pulmonary embolism, COPD, and community-acquired pneumonia. By doing so, we strive to provide valuable insights for clinicians, policymakers, and healthcare providers to improve patient care, optimize resource allocation, and enhance the overall efficiency and effectiveness of public healthcare systems.

Through the exploration of modifiable and non-modifiable predictors, this research aims to generate evidence-based recommendations and strategies that will positively impact patient outcomes and healthcare management in the context of an aging population with complex chronic conditions.

**Figure 1. Average length of stay in hospital, 2000 and 2020**




Source: OECD Health Statistics 2020; Eurostat Database.

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# CHAPTER II

## Risk factors for hospital outcomes in pulmonary embolism: a retrospective cohort study

# Risk factors for hospital outcomes in pulmonary embolism: a retrospective cohort study

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## Abbreviations

| | |
|---|---|
| **BMI** | Body mass index |
| **BP** | Blood pressure |
| **BPM** | Beats per minute |
| **CI** | Confidence interval |
| **CTPA** | Computed tomography pulmonary angiogram |
| **DVT** | Deep vein thrombosis |
| **GP** | General practitioner |
| **HR** | Heart rate |
| **ICD** | International Classification of Diseases |
| **IQR** | Interquartile range |
| **IRR** | Incident risk ratio |
| **KSBL** | (Kantonsspital Baselland) cantonal hospital of Baselland |
| **LOHS** | Length of hospital stay |
| **NT-proBNP** | N-terminal pro b-type natriuretic peptide |
| **OR** | Odds ratio |
| **PE** | Pulmonary embolism |
| **PESI** | Pulmonary Embolism Severity Index |
| **ROC** | Receiver operating characteristic |
| **SD** | Standard deviation |
| **VTE** | Venous thromboembolism |

**Abstract**

**Background**: Pulmonary embolism (PE) is not only a life-threatening disease but also a public health issue with significant economic burden. The aim of the study was to identify factors—including the role of primary care—that predict length of hospital stay (LOHS), mortality and re-hospitalization within 6 months of patients admitted for PE.

**Method**: A retrospective cohort study was conducted with patients presenting to a Swiss public hospital with PE diagnosed at the hospital between November 2018 and October 2020. Multivariable logistic and zero-truncated negative binomial regression analyses were performed to assess risk factors for mortality, re-hospitalization and LOHS. Primary care variables encompassed whether patients were sent by their general practitioner (GP) to the emergency department and whether a GP follow-up assessment after discharge was recommended. Further analyzed variables were pulmonary embolism severity index (PESI) score, laboratory values, comorbidities, and medical history.

**Results**: A total of 248 patients were analyzed (median 73 years and 51.6% females). On average patients were hospitalized for 5 days (IQR 3–8). Altogether, 5.6% of these patients died in hospital, and 1.6% died within 30 days (all-cause mortality), 21.8% were re-hospitalized within 6 months. In addition to high PESI scores, we detected that, patients with an elevated serum troponin, as well as with diabetes had a significantly longer hospital stay. Significant risk factors for mortality were elevated NT-proBNP and PESI scores. Further, high PESI score and LOHS were associated with re-hospitalization within 6 months. PE patients who were sent to the emergency department by their GPs did not show improved outcomes. Follow-up with GPs did not have a significant effect on re-hospitalization.

**Conclusion**: Defining the factors that are associated with LOHS in patients with PE has clinical implications and may help clinicians to allocate adequate resources in the management of these patients. Serum troponin and diabetes in addition to PESI score might be of prognostic use for LOHS. In this single-center cohort study, PESI score was not only a valid predictive tool for mortality but also for long-term outcomes such as re-hospitalization within 6 months.

## 1. Introduction

Pulmonary embolism (PE) is a serious, potentially life-threatening health condition that represents the third major cause of cardiovascular death behind myocardial infarction and cerebrovascular accidents (1, 2). PE can be considered a central public health issue since it is associated with a substantial economic burden (3–6).

The exact incidence rate for PE is not available but estimates range from 39 to 115 per 100,000 population. Additionally, as the incidence of PE rises with age, PE rates can be expected to continue increasing even further due to the rapidly ageing population in high-income countries, and therefore to significantly impact morbidity, mortality, and healthcare costs (6, 7). Most nations have an urgent dilemma in the realm of public health: how to address the difficulties brought on by the rise in the number of PE patients while utilizing the available medical resources to better fulfill their medical demand without impacting on cost and overtreatments.

Over the past decades, the incidence rate of PE has increased in Europe, whereas the mortality rate and the length of hospital stay (LOHS) have slightly decreased, due to advances in treatments and diagnostics (8–12). In a retrospective, Italian cohort study of 328 patients with PE, despite a trend in reduction in LOHS, the mean and median have not significantly decreased, due to a very small percentage (3%) of patients who received an ultra-early discharge and a large percentage of patients who were discharged within 6 days (31.5%) (13). LOHS is considered a crucial characteristic for health reports when it comes to the management and evaluation of inpatients and is a significant signal for the assessment of hospitals' service quality (14). Several factors can influence LOHS in patients with PE such as sociodemographic, health-related characteristics and hospital care-related features (15–17). Due to the wide variability of influencing factors, there is no uniform approach to predict the length of stay for PE.

The primary aim of the study was to identify which factors may affect the length of stay of patients admitted for PE. The identification of patient characteristics influencing LOHS may allow decision-makers to plan hospital management accordingly.

Particularly we retrospectively explored if the primary outcome length of hospital stay for PE was influenced by commonly available sociodemographic and health-related variables measurable at entry time.

Although a reduced length of stay decreases hospital costs, it might negatively affect the quality of care. For this reason, as secondary outcomes, we analyzed factors associated with all-cause mortality (in hospital or 30 days mortality) and rehospitalization within 6 months.

## 2. Materials and methods

*Design and setting*

Our study was conducted in the cantonal hospital of Baselland (KSBL), a district general hospital covering a stable population of 280,000 in Northwest Switzerland. We undertook a retrospective cohort study with 378 consecutive patients hospitalized at the KSBL at the medical or surgical ward and who received the diagnosis of pulmonary embolism (according to the primary International Classification of Disease codes) during their hospital stay between November 2018 and October 2020. We were able to access the electronic case notes of 378 patients to retrieve presenting symptoms and clinical signs that have been associated with PE. Further, socio-demographics, vital signs, comorbidities and discharge variables (mortality and re-hospitalization) were assessed.

*Inclusion and exclusion criteria*

Data of these patients were individually reviewed. Patients were included in the study if a new PE was the main reason for their hospitalization and their diagnosis was confirmed by computer tomographic pulmonary angiogram (CTPA), scintigraphy or duplex ultra-sound by a specialist (deep vein thrombosis (DVT) combined with PE specific symptoms) within 12 h after presentation. Alternatively, they were also included if confirmatory, diagnostic imaging was performed later, but anticoagulant treatment was started within 12 h after presentation to the hospital due to high clinical suspicion of PE.

The following patients were excluded:

- Denied research consent.
- PE only as a suspected diagnosis and never confirmed with any imaging method.
- Primarily hospitalized for another reason, and PE was diagnosed after >12 h.
- Transferred from/to another hospital and therefore no complete case documentation.

After the application of the eligibility criteria, 248 patients were included in the analysis.

*Statistical analyses*

The outcome variables comprised LOHS (primary outcome), all-cause mortality in hospital and 30 days, and re-hospitalization within 6 months (secondary outcomes).

To minimize the risk of bias, optimism, and overfitting, no data-driven selection of variables was done. We selected potential predictors based on the literature and on clinical knowledge. Two researchers conducted a literature review and consulted clinical experts in the field. All variables are included in Table 1. Predictors included the PESI score based on age at entry, sex, history of cancer, history of chronic lung disease, history of heart failure, respiratory rate, hypothermia (below 36 degrees Celsius), systolic blood

pressure (BP) <100 mmHg, heart rate (HR) ≥110 bpm, O2 saturation (SpO2) below 90%, altered mental status, and respiratory rate ≥ 30/min (18).
Other variables of interest were body mass index (BMI), a medical history of dyslipidemia, diabetes, or previous PE. Laboratory values of interest were serum N-terminal pro B-Type natriuretic peptide (NT-proBNP) and Troponin-T high-sensitive (hs). The analysis of LOHS was primarily on patients that were discharged alive, a sensitivity analysis was performed on the full data set.
Further, the housing situation before admission and admission via another doctor (usually the GP) were entered into the models. For re-hospitalization outcome, we further entered the variable if GP follow-up was suggested and the LOHS.
For descriptive statistics as measures of central tendency, we displayed mean and standard deviation (SD) in case of normal distribution and median with interquartile range in case of skewed distribution, which was assessed through histograms assessment. For categorical variables we reported absolute and relative frequencies.
Variables with missing values were imputed using the k-Nearest Neighbor algorithm [function knn.impute from the R package "bnstruct" (19)]. A zero-truncated negative binomial regression was conducted to estimate the LOHS and its association with potential risk factors using the R package "VGAM." As a sensitivity analysis, all regression models were additionally performed on the original, non-imputed data set.
Logistic regression models were created to estimate the risk of death and rehospitalization, and its association with potential risk factors.
All statistical analyses were performed using R, version 4.0.3 statistical software (R Foundation for Statistical Computing). All p-values reported were 2-sided; statistical significance was defined as $p < 0.05$.

## 3. Results

*Patient characteristics*

A total of 378 patients were identified who received the diagnosis of pulmonary embolism during their hospital stay. After the exclusion of 24 patients who declined research consent, 15 patients in which the diagnosis was not confirmed with imaging methods, 67 patients who were diagnosed more than 12 hours after admission, and a further 24 who had incomplete diagnostic documentation, 248 cases were analyzed. The patient characteristics are shown in Table 1.

**Table 1:** Patient characteristics

| | all (n=248) | Missing n (%) |
|---|---|---|
| **Demographic** | | |
| Age at diagnosis, median (IQR) in years | 73 (62-81.5) | -- |
| Gender (Female) | 128 (51.6 %) | -- |
| Insurance type | | |
| General | 199 (80.2%) | -- |
| Half-private | 30 (12.1%) | -- |
| Private | 19 (7.7%) | -- |
| **Vital Signs** | | |
| Heart rate (bpm), mean (SD) | 92.1 (19.7) | -- |
| Tachycardia (>100 bpm) | 76 (30.6 %) | -- |
| Blood pressure systolic (mmHg), mean (SD) | 140.7 (24.9) | -- |
| Blood pressure diastolic (mmHg), mean (SD) | 83.1 (14.1) | -- |
| Hypotension (<100/60 mmHg), n (%) | 11 (4.4%) | -- |
| Hypertension (>140/90 mmHg), n (%) | 124 (50%) | -- |
| Respiratory rate (/min) mean (SD) | 20.4 (5.7) | 35 (14.1%) |
| Hypothermia (<36 °C), n (%) | 9 (3.6%) | -- |
| Oxygen saturation, mean (SD) | 93.8 (4.8) | -- |
| Oxygen requirement | 36 (14.5%) | -- |
| **Comorbidities** | 229 (92.3%) | -- |
| Dyslipidemia, n (%) | 44 (17.7%) | -- |
| Diabetes, n (%) | 37 (14.9%) | -- |
| Cardiovascular disease, n (%) | 86 (34.7%) | -- |
| Heart failure, n (%) | 5 (2%) | -- |
| Chronic lung disease, n (%) | 44 (17.7%) | -- |
| Rheumatic disease, n (%) | 30 (12.1%) | -- |
| Mental disease, n (%) | 55 (22.2%) | -- |
| Altered mental status, n (%) | 5 (2.2%) | -- |
| Active cancer, n (%) | 30 (12.1%) | -- |
| **Medical history** | | |
| Previous VTE, n (%) | 58 (23.4%) | -- |
| Previous PE, n (%) | 26 (10.5%) | -- |
| Previous DVT, n (%) | 44 (17.7%) | -- |
| History of cancer, n (%) | 50 (20.2%) | -- |
| History of hypertension, n (%) | 126 (50.8%) | -- |
| **PESI** | | |

| | | |
|---|---|---|
| PESI score, mean (SD) | 96.8 (31.4) | -- |
| PESI retrospectively calculated, n (%) | 200 (81%) | |
| **Laboratory Values** | | |
| NT-proBNP, (ng/l) median (IQR) * | 499 (125-2479) | 70 (28.2%) |
| Troponin-T hs (ng/l), median (IQR) ** | 16.95 (7.22-44.38) | 94 (37.9%) |
| **Entry and discharge circumstances** | | |
| Housing situation before admission | | |
| Private home, n (%) | 211 (85.1%) | -- |
| Care facility, n (%) | 37 (14.9 %) | -- |
| Sent by GP, n (%) | 122 (49.2%) | -- |
| Follow-up with GP, n (%) | 72 (29 %) | -- |
| Discharge destination | | -- |
| Private home, n (%) | 200 (80.6%) | |
| Care facility, n (%) | 34 (13.7%) | |
| Rehabilitation unit, n (%) | 21 (8.5%) | -- |
| **Outcomes** | | |
| Length of stay, in nights, median (IQR) | 5 (3-8) | -- |
| Rehospitalization at KSBL within six months after discharge, n (%) | 51 (21.8%) | -- |
| Death | 18 (7.3%) | -- |
| Death (in hospital death) | 14 (5.6%) | -- |
| Death (30 days mortality) | 4 (1.6%) | -- |

* NT-proBNP normal range <125 ng/l
** Troponin-T hs <14 ng/l

The median age at admission was 73 years (range 19-96) and 51.6% were female. The majority of the patients had general insurance (80%). Vital signs measured at admission revealed that the mean HR was 92.1 but one third of the patients presented to the hospital with tachycardia (30.6%). The average blood pressure was 141/83 mmHg, while half of the patients had hypertension while only a minority of the patients had hypotension, (4.4%). The body temperature was usually in the normal range and oxygen saturation was on average 93.7%, but some of the patients needed oxygen supply at entry (14.5%).

The majority of the patients had comorbidities (92.3%), the three most frequent disease types were: cardiovascular (34.7%), mental (22.2%) and chronic lung diseases (17.7%). Patients' history revealed that previous VTE occurred in 23.4%, the most frequent one was DVT, followed by PE whereas 12 patients had both (4.8%).

PESI score was calculated at admission in 19% of the cases, in the remaining 81% of the cases the PESI score was calculated retrospectively. The mean of the PESI score was 96.8 (SD = 31.4). Regarding the laboratory values, NT-proBNP was measured in 71.8% of the patients and the values had a median of 499 ng/l (IQR 125-2479), whereas troponin-T hs was measured in 62% of the patients with a median of 16.9 ng/l (6.84-46.2)

Before admission most of the patients lived independently, but 14.9% were admitted from a care facility. Almost half of the patients were sent to the hospital by a GP (49.2%). After the discharge, a follow-up with a GP was organized in 29% of all cases. The majority of the patients returned to their private homes (80.6%) while 13.7% were transferred to a care facility or a rehabilitation center (8.5%).

Out of 248 hospitalized patients with pulmonary embolism, 14 patients died during the hospital stay and were excluded from regression analyses with outcome LOHS and re-hospitalization. Patients with PE who did not die within the hospital stayed for a median of 5 days (IQR 3-8). Additionally, 4 patients died within 30 days (1.6 % of the total patients) and rehospitalization at KSBL within 6 months after discharge occurred in 21.8% of the cases.

*Prediction of LOHS*

Our primary aim was to identify factors that predict LOHS. Table 2 provides coefficient estimates for predictors of LOHS in patients who did not die. Regression coefficients are shown as incident risk ratio (IRR). Patients with higher PESI scores (IRR = 1.068, 95%CI [1.034-1.104], p-value <0.001), higher troponin values (IRR = 1.433, 95%CI [1.189-1.727], p-value <0.001), and with diabetes (IRR = 1.293, 95%CI [1.007-1.66], p-value 0.044) had significantly longer LOHS.

The LOHS prediction at the intercept (5.899 days) is the LOHS when all covariates are at 0 (for categorical covariates) or at their mean (for continuous covariates). The predicted LOHS of the model for each variable is presented for one unit increase. If the PESI score increases by 1 unit (on the original scale per 10 points), the predicted LOHS increases from 5.89 to 6.27 days. A higher increase occurs when the Troponin increases by 1 unit (on the original scale per 100 n/L) the predicted LOHS rise to 8.3 days. People with diabetes compared to those without tend to stay 2 nights longer, assuming all other variables are held constant.

**Table 2**: Results of multivariable zero-truncated negative binomial regression model for length of hospital stay (LOHS) estimation in pulmonary embolism survivors (n = 234).

| | LOHS prediction | IRR (95%CI) | p-value |
|---|---|---|---|
| (Intercept):1 | 5.899 | 2.422 (1.742-5.722) | 0.004 |
| **PESI score (per 10 points)** | **6.273** | **1.068 (1.034-1.104)** | **<0.001** |
| NT-proBNP (per 1000 units) | 6.012 | 1.021 (0.997-1.045) | 0.089 |
| **Troponin-T hs (per 100 units)** | **8.297** | **1.433 (1.189-1.727)** | **<0.001** |
| Pervious PE | 6.485 | 1.107 (0.829-1.478) | 0.492 |
| Previous DVT | 5.482 | 0.924 (0.724-1.178) | 0.522 |
| **Diabetes** | **7.517** | **1.293 (1.007-1.66)** | **0.044** |
| Cardiovascular diseases | 6.904 | 1.183 (0.969-1.443) | 0.098 |
| Dyslipidemia | 5.041 | 0.842 (0.66-1.075) | 0.168 |
| BMI | 6.039 | 1.026 (0.87-1.209) | 0.763 |
| Housing situation before admission | 5.104 | 0.854 (0.656-1.112) | 0.241 |
| Sent by doctor | 5.98 | 1.015 (0.846-1.217) | 0.873 |

Our secondary aims included the analyses of factors associated with mortality and rehospitalization rates. The results of the univariate logistic regression models for mortality, adjusted for PESI score, are displayed in table 3. Higher PESI scores and NT-proBNP values were significantly associated with mortality in patients with pulmonary embolism (OR 1.617, 95%CI [1.359-1.981], p-value <0.001 and OR 1.091, 95%CI [1.012-1.171]p-value 0.013 respectively). No other variable was found to be statistically significant in the association with the mortality rate.

**Table 3:** Results of univariate logistic regression model for mortality (in-hospital or within 30 days) in pulmonary embolism (n = 18). All variables were adjusted for PESI score.

| | OR (95%CI) | p-value |
|---|---|---|
| **PESI score** | **1.617 (1.359-1.981)** | **<0.001** |
| **NT-proBNP** | **1.091 (1.012-1.171)** | **0.013** |
| Troponin-T hs | 0.139 (0.003-1.949) | 0.249 |
| Previous DVT | 0.41(0.022-2.322) | 0.408 |
| Diabetes | 0.782 (0.152-2.979) | 0.74 |
| Cardiovascular diseases | 1.628 (0.537-5.073) | 0.388 |
| Dyslipidemia | 0.341 (0.043-1.611) | 0.229 |
| BMI | 0.443 (0.117-1.399) | 0.199 |
| Housing situation before admission (care facility) | 1.443 (0.367-4.715) | 0.575 |
| Sent by doctor | 1.423 (0.454-4.715) | 0.548 |
| LOHS | 1.056 (0.967-1.137) | 0.172 |

The results of our secondary multivariable analysis concerning rehospitalization rate are reported in table 4. The odds for rehospitalization within 6 months in KSBL were also significantly higher for patients with a higher PESI score and for patients with a higher LOHS (OR 1.183, 95%CI [1.041-1.353] p-value 0.012 and OR 1.099, 95%CI [1.031-1.183] p-value 0.007 respectively). No other variable was found to be statistically significant in the association with rehospitalization.

**Table 4:** Multivariable logistic regression model for rehospitalization in pulmonary embolism.

| | **OR (95%CI)** | **p-value** |
|---|---|---|
| **PESI score** | **1.183 (1.041-1.353)** | **0.012** |
| NT-proBNP | 0.934 (0.831-1.03) | 0.546 |
| Troponin-T hs | 0.853 (0.265-1.926) | 0.957 |
| Previous PE | 0.522 (0.116-1.772) | 0.339 |
| Previous DVT | 1.346 (0.495-3.456) | 0.545 |
| Diabetes | 1.917 (0.733-4.893) | 0.175 |
| Cardiovascular diseases | 1.871 (0.873-4.013) | 0.106 |
| Dyslipidemia | 0.525 (0.181-1.372) | 0.208 |
| BMI | 0.747 (0.36-1.437) | 0.404 |
| Housing situation before admission (care facility) | 0.815 (0.279-2.139) | 0.69 |
| Sent by doctor | 1.019 (0.501-2.076) | 0.959 |
| Follow up with GP | 1.352 (0.626-2.869) | 0.435 |
| **LOHS** | **1.099 (1.031-1.183)** | **0.007** |

## 4. Discussion

This retrospective observational cohort study of patients with PE showed that LOHS is influenced by PESI score, serum troponin values and diabetes. Other factors such as medical history, other types of comorbidities and whether the patients were sent to the hospital by a GP were not associated with longer LOHS.

PESI score is a validated prognostic model for PE devised by Aujesky and colleagues. (20) Originally it was developed to predict 30-day mortality using 11 clinical criteria (age at entry, sex, history of cancer, history of chronic lung disease, history of heart failure, respiratory rate, hypothermia [below 36 degrees Celsius], systolic blood Pressure (BP) <100 mmHg, heart rate (HR) ≥110 bpm, oxygen saturation below 90 percent, altered mental status, and respiratory rate ≥30 breaths per minute (20)). The PESI score was also implemented to identify low-risk patients who might be treated outside the hospital and consequently be eligible for early discharge. (18) In line with other studies, our results also confirm the prognostic validity of the PESI score in predicting the length of hospital stay. (21, 22) The role of PESI in LOHS was confirmed by Rodriguez et al. (23), however the impact of the single items composing the score was unclear. For this reason, in our study, we have also analyzed the items of the PESI score separately and we found that age, sex heart rate over 110 bpm, oxygen saturation < 90 percent and heart failure were significantly predictive for LOHS (for more details see table 5 in the appendix).

A strong finding of our research is that serum troponin was statistically significant in association with LOHS, despite the model being controlled for cardiovascular disease. This trend was noted by Muktar et al. in 2018 where patients who had long LOHS had higher values of cardiac biomarkers compared to those with short LOHS, but no statistically significant difference was found in their study, possibly due to the small sample size (22). Elevated cardiac troponins are known to indicate subendothelial ischemia in the right ventricle (24) and to be associated with right ventricular dysfunction and pulmonary hypertension in acute PE (25, 26). These complications may explain the found association with extended LOHS.

Another point worth discussing is the fact that diabetes was the only health condition associated with longer LOHS. Previous studies have investigated the relationship between diabetes and PE incidence (27) or demonstrated that patients with diabetes have worse outcomes compared to patients without diabetes, especially in terms of mortality (28) or hospitalization rate (29). A recent study by Schmitt et al. found that PE patients with diabetes had prolonged LOHS (30), which is confirmed by our results. So, despite advances in treatments, diabetes is still associated with a higher risk of adverse outcomes and healthcare providers should take this finding into account. Although PE patients who also suffer from diabetes are at elevated risk for adverse events and a complicated clinical course (30, 31), further studies are required in order to clarify the underlying mechanisms and impact of disturbed glucose metabolism on the generation and clinical outcome of PE in light of LOHS.

The study followed up patients until late 2020 (the first year of the COVID-19 pandemic), however only one case out of 248 in our sample was tested positive for the SARS-CoV-2 virus. The reason why the proportion of patients with a positive test is low relies on our inclusion criteria, since we selected patients who were hospitalized with pulmonary embolism as their main diagnosis (reason for hospitalization). The majority of patients hospitalized with COVID-19 received a different ICD code as their main diagnosis and are not captured in our cohort.

Our secondary aim was to assess which factors were associated with morality rate. The overall in-hospital (5.6%) and the 30-days mortality rate (5.6% and 1.6%) observed in this study, were relatively low compared to that reported in recent studies by Matskiv et al. and by Jiménez et al. (32) (11.9% and 5.4% respectively). Our results showed that mortality was associated with elevated values of NT-proBNP in addition to the PESI score. As previously stated, the PESI score is the most validated prognostic model for PE in predicting mortality and our study confirms this association and is in line with previous publications. (17, 18, 20, 21, 33, 34)

The role of biomarkers in all-cause mortality of patients with pulmonary embolism has been debated. A meta-analysis by Lega et al. (35) showed that higher level of NT-proBNP was associated with higher risk of adverse outcomes, all-cause mortality among them. Interestingly in our research, we detected a difference between the role of NT-proBNP and troponin values. As previously discussed, our study revealed that higher serum troponin was significantly associated with LOHS whereas NT-proBNP was associated with mortality. The meta-analysis of Klok et al. (36) found that high concentrations of BNP in PE patients were associated with complicated in-hospital course and death, while LOHS was analyzed in particular. Another meta-analysis by Beccatini et al. (37) showed that elevated values of troponin were indicator of high risk for short-term death in patients with acute PE, but the study limited his research to troponin values only and did not include NT-proBNP values. In a recent Swiss study by Benmachiche et al. (38) results revealed that patients with high levels of NT-proBNP were at higher risk of in-hospital mortality and longer LOHS, regardless of their clinical characteristics. Although in other conditions like acute coronary syndrome, the level of NT-proBNP provided better predictive power than troponin (39), this difference in PE patients has still to be established. Ultimately, the precise role of biomarkers in early risk stratification is fundamental since PE may present with a wide spectrum of symptoms but in some cases with no evident symptoms. Biomarkers might be fundamental in order to detect a serious condition and allow consequently treatment adjustment with more aggressive therapy.

Our secondary outcomes included rehospitalization rates. We detected that in our study population rehospitalization within 6 months was significantly influenced by PESI score and in addition by LOHS but not by other factors. PESI score has been validated in studies with a relatively short-term follow-up (30 days and 90 days mortality), (17, 40, 41) one study showed its accuracy in predicting long-term prognosis

(6month and 1 year mortality) (33) but its accuracy in predicting long term outcome in terms of rehospitalization in 6 months has not been established. The role of LOHS and its association with the risk of rehospitalization has been debated in research (42–45). Literature suggests that both short length of stay and long length of stay can be associated with rehospitalization rates. On one hand, a shortening of the length of stay could point to the so colloquially called "bloody" discharges, where the patient is not yet in a sufficient state of health or still has open problems. (46, 47) On the other hand, a longer length of stay could be associated with rehospitalizations because it could occur especially in critically ill people and multimorbid elderly patients, who are subsequently exposed to a higher risk of readmission (42, 44). In order to test the association of LOHS with rehospitalization we visualized the frequency of rehospitalization versus LOHS and detected rather a linear tendency, as the LOHS increased so did the percentage of rehospitalization rates. (Figure 1) For the above-mentioned reasons, we included LOHS in our model as a continuous variable and did not dichotomize it in short versus long length of hospital stay. The explanation for such tendency is that patients with pulmonary embolism hospitalized in KSBL are on average old and multimorbid patients. The positive aspect of these results is that patients were usually not discharged too early, and a short length of stay did not result in a higher risk of rehospitalization.

In all our analyses the PESI score had significant influence on LOHS, mortality and rehospitalization. PESI score is an essential parameter for determining how to proceed with the patient (e.g. outpatient treatment, surveillance). (48) Therefore, whenever it is not calculated, the patient is at risk of being under- or overtreated. By definition, the PESI score is used to predict 30-day mortality and is a widely validated model that uses clinical parameters to stratify patients into five risk levels. (20).Unfortunately, in our study PESI score was only calculated at the time of admission in 19% of the cases, in the remaining 81% of the cases the PESI score was calculated retrospectively.

Published audits on the management of PE patients only cover very particular aspects of the process, for instance, the use of clinical decision rules (49) or treatment strategies (50) or only look at single subsegmental PE (51) and do not focus on the frequency of the PESI score calculation. Therefore, do not know if the proportion is representative of usual practice. In our opinion, the fact that the PESI score is poorly reported can be due to two factors: either other indicators are given priority in the emergency department, or the PESI was actually calculated but not entered into the patients' records.

The criteria that make up the score refer to easily accessible information and vital signs that can be measured by a GP. Moreover, the score is of high importance in predicting not only severity and mortality but also LOHS and the likelihood of re-hospitalization. Therefore, we believe that it may be appropriate for GPs who suspect pulmonary embolism to already calculate the PESI when sending a patient to the hospital.

*Comparison between multivariable models and sensitivity analysis*

In our study we assessed the association between PESI score in addition to other risk factors and we also assessed the parameters composing the PESI score alone. As displayed in the Appendix Figure 2 LOHS prediction the receiver operating characteristic (ROC) curve shows a higher accuracy for the model with other parameters in addition to PESI score compared to the model with PESI score alone and this is valid both for 5 days prediction (median LOHS) and for 8 days prediction (the upper IQR).

The sensitivity analysis on the full data for the prediction of LOHS did not give any other predictor except for NT-proBNP which was predictive for in-hospital death. The sensitivity analysis on the full data for the prediction of the PESI items only on LOHS shows the same results as the analysis performed on the patients that were discharged alive.

*Strengths, limitations, and further research*

Despite the availability of a large amount of data regarding the prognosis of PE patients, only a few studies have investigated possible predictors of LOHS in these patients (15, 21, 52). The novelty of our study is that the analysis did not limit its focus just to the PESI score. Our analysis looked at a broader range of variables (demographic, health-related risk factors and the role of primary care) as well as the PESI score and determined their associations with outcomes of interest. The data collection involving manual extraction of information was conducted by a doctor alone but subsequently, the parameters forming the PESI score were reviewed independently by two researchers. The characteristics of the sample of this study are comparable with other cohorts with a bigger sample size, for example in our study the median age was 73 years 52% were female and 50% had hypertension as a comorbidity. In a German study from 2018 with almost one million PE patients, the median age was 72, 54% were female and 43% had hypertension. (8).

All statistical analyses that were primarily performed on imputed data have also been applied to the non-imputed dataset, the statistical significance of the variables with missing data did not differ in the two models. The sensitivity analysis demonstrated that the internal validity of our research was not impacted by missing data.

There are some limitations to this study. As a retrospective study design, the data quality depends on precise documentation in the patient files. Particularly we assumed that if the PESI score was not reported, the clinician did not calculate it, so we could have underestimated the percentage of patients with a PESI calculation at entry to hospital. Additionally, information about rehospitalization within 6 months was only possible within KSBL: due to privacy policy, it was not possible to access information about rehospitalizations in other hospitals. However, in Switzerland readmissions usually occur within the same hospital; a Swiss study has shown that only 17% of unplanned readmissions occurred at a different hospital. (42) Our results concerning mortality and rehospitalization rates must be interpreted carefully since their occurrence was relatively low (18 and 51 patients, respectively).

Further research to prospectively validate the statistical model's accuracy in predicting LOHS - ideally in multicenter studies with a larger sample size - is needed.

## 5. Conclusion

Understanding the factors that are associated with LOHS in patients with PE has clinical implications and may help healthcare providers to deliver efficient care and to allocate adequate resources in the management of these patients. In summary, the results of this study showed that the PESI score is a major predictor of LOHS, mortality and rehospitalization in PE patients. Diabetes is an additional risk factor that healthcare providers should be aware of. Even though cardiac biomarkers and comorbidities are predictors of LOHS, their role in defining mortality and rehospitalization is yet to be established. Moreover, our study confirmed the essential role of PESI score calculation in the management of PE patients, clinicians and GPs should be aware of and perform the calculation as soon as PE is diagnosed.

## 6. Appendix

Supplemental Table

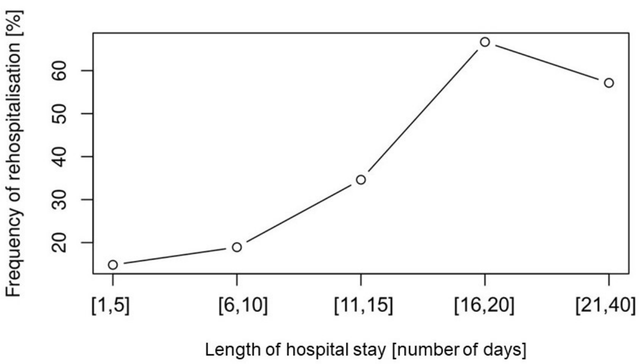
Table 5: Multivariable zero-truncated negative binomial regression model for length of hospital stay (LOHS) estimation in pulmonary embolism survivors with PESI items separately assessed (n = 234).

| | **LOHS prediction** | **IRR (95%CI)** | **p-value** |
|---|---|---|---|
| Intercept | 4.638 | 1.774(1.148-2.742) | 0.01 |
| **Age** | **5.207** | **1.138 (1.071-1.21)** | **<0.001** |
| **Sex** | **5.864** | **1.296 (1.083-1.55)** | **0.005** |
| History or active cancer | 4.72 | 1.02 (0.829-1.255) | 0.851 |
| BP systolic <100 mmHg | 5.452 | 1.197 (0.761-1.883) | 0.436 |
| **Heart rate ≥110 bpm** | **6.139** | **1.361 (1.075-1.724)** | **0.01** |
| Respiratory rate ≥30 breaths/min | 4.876 | 1.058 (0.707-1.583) | 0.783 |
| **Oxygen <90%** | **6.188** | **1.373 (1.109-1.699)** | **0.004** |
| Chronic lung disease | 5.107 | 1.114 (0.878-1.414) | 0.375 |
| Altered mental status | 5.003 | 1.089 (0.51-2.324) | 0.826 |
| Hypothermia<36°C | 4.821 | 1.045 (0.612-1.782) | 0.872 |
| **Heart failure** | **9.345** | **2.113 (1.165-3.832)** | **0.014** |

The analysis of the items composing the PESI score showed that age, sex, heart rate over 110 bpm, oxygen saturation < 90 percent and heart failure were significantly associated with LOHS.

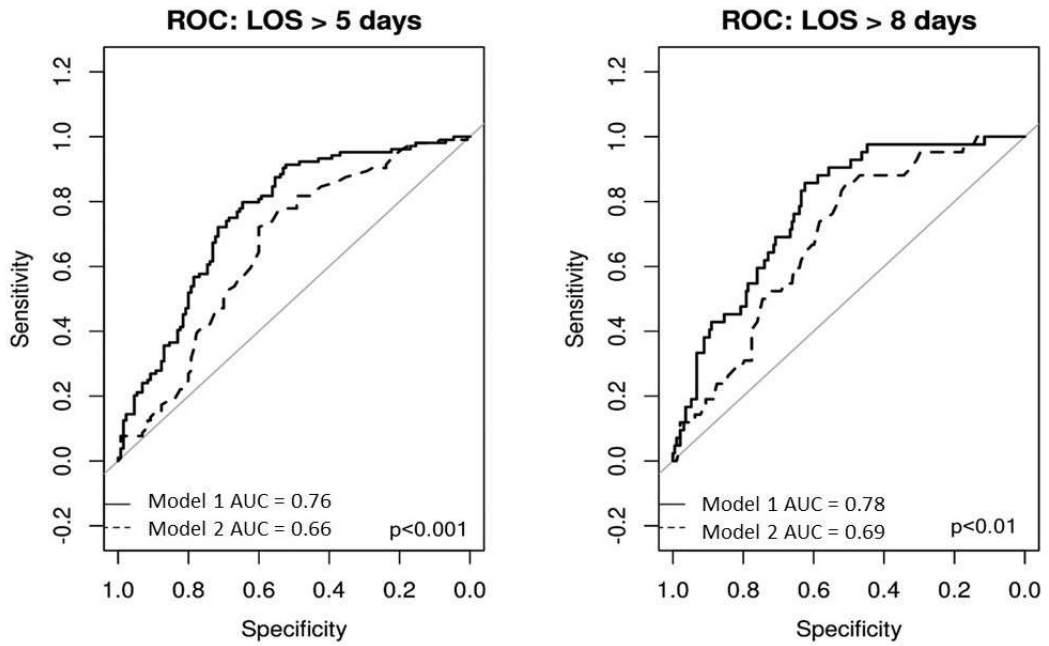
Supplemental Figures

**Figure 1:** Frequency of rehospitalization versus length of hospital stay (LOHS)




Rehospitalization rates increases with longer length of hospital stay in approximately lineal relationship.

**Figure 2:** Receiver operating characteristic (ROC) curve accuracy of the models to predict 5 days and 8 days length of hospital stay




For both 5 days and 8 days prediction, model 1 showed higher accuracy than model 2.

Model 1 includes the following variables: PESI score, BMI, a medical history of dyslipidemia, diabetes or previous PE, NT-proBNP and troponin-T hs, housing situation before admission and admission via GP. Model 2 only includes the PESI score.

PESI score is based age at entry, sex, history of cancer, history of chronic lung disease, history of heart failure, respiratory rate, hypothermia [below 36 degrees Celsius], systolic blood pressure (BP) <100 mmHg, heart rate (HR) ≥110 bpm, oxygen saturation below 90 percent, altered mental status, and respiratory rate ≥30 breaths per minute. (18)

**Statement of Ethics**

The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association. This study protocol was reviewed and approved by Nordwest- and Zentralschweiz ethic commission (Project-ID 2021-00964).

**Conflict of Interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Author Contributions

G. Lüthi-Corridori and C. Kueng were responsible of data collection. G. Lüthi-Corridori, S. Giezendanner and M. Boesing were responsible for data analysis. G. Lüthi-Corridori S. Giezendanner and J.D. Leuppi were responsible for designing the study. All authors contributed to writing the manuscript and agreed to be accountable for the content of the work.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## Data Availability Statement

All data generated were analyzed during this study and the results included in this article. Further inquiries can be directed to the corresponding author.

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# CHAPTER III

## Predictors of length of stay, rehospitalization and mortality in CAP patients: a retrospective cohort study

# Predictors of length of stay, rehospitalization and mortality in CAP patients: a retrospective cohort study

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**Abstract**

Background: Community acquired pneumonia (CAP) represents one of the leading causes of hospitalization and has a substantial impact on the financial burden of healthcare. The aim of the study was to identify factors associated with the length of hospital stay (LOHS), re-hospitalization and mortality of patients admitted for CAP.

Methods: A retrospective cohort study was conducted with patients presenting to a Swiss public hospital between January 2019 and December 2019. Zero-truncated negative binomial and multivariable logistic regression analyses were performed to assess risk factors.

Results: A total of 300patients were analyzed (median 78 years and 53% males) with an average LOHS of 7 days. 31.6% were re-hospitalized within 6 months, 2.7% of the patients died within 30-days and 11.7% died within 1 year. The results showed that sex, age, qSOFA score and atypical pneumonia were predictive of LOHS. Diabetes, higher qSOFA score and rehabilitation after discharge were associated with a higher chance to be rehospitalized within 6 months, whereas mortality within 30-days and within one year were both associated with older age and the presence of a cancer diagnosis.

Conclusion: This study identified routinely available predictors for LOHS, rehospitalization and mortality in patients with CAP, which may further advance our understanding of CAP and thereby improve patient management, discharge planning, and hospital costs.

## 1. Introduction

Community acquired pneumonia (CAP) is one of the leading causes for hospitalization and responsible for approximately 2.5 million deaths worldwide every year. [1,2] In Europe CAP also leads to high hospitalization rates causing a significant financial burden for the healthcare system. [3,4] The financial impacts of CAP due to prolonged hospitalizations or increased hospitalization rates, has been documented in previous studies. [5–7] Current guidelines emphasize the importance of discharging patients as soon as they achieve clinical stability and have access to a safe environment where continuity of care can be ensured. [8] The recommendations particularly underline the importance of increasing outpatient treatment to decrease cost of hospitalizations and risk of hospital-acquired complications. [8] However, length of hospital stay (LOHS) in patients with CAP continue to be variable and for that reason, the development of accurate models to predict LOHS using patients` baseline profiles from an early stage is needed. Obtaining accurate predictive models upon admission has multiple advantages. First of all, they allow us to identify profiles of patients at risk of prolonged hospitalization and whenever possible, to promptly act on modifiable factors. Moreover, discharge strategies can be improved. The implementation of a precise prediction model would additionally permit the evaluation of hospital performance, thereby fostering advancements in hospital management.

LOHS in patients with CAP can be influenced by a variety of factors, including sociodemographic, health-related and hospital care-related characteristics. [9-21]

A number of previous studies investigating factors that influence LOHS in CAP identified patient related variables such as advanced age and specific comorbidities in addition to disease severity as predictors of prolonged LOHS. [9–13] Other studies direct their research focus on laboratory values [14–16] while others concentrate on therapies [17–19] or other interventions during hospitalization. [20,21] Due the wide variability of influencing factors, there is no uniform method for predicting LOHS in CAP patients, moreover, as mentioned above several studies included factors that are not available at admission time, hindering the chance of predicting LOHS on the first days of hospitalization.

The primary aim of this study was to identify which factors may affect the length of stay of patients admitted for CAP. The identification of patient characteristics influencing LOHS may help decision-makers to properly plan hospital management. Particularly, we retrospectively explored if the primary outcome LOHS for CAP was associated with commonly available sociodemographic and health-related variables measurable at the time of admission to hospital.

Despite advances in therapy, the mortality rate associated with this disease is still high (6-10%). While a shorter LOHS may decrease hospital costs, it may also negatively impact the quality of care. [22] Moreover research has indicated that rehospitalization and mortality rates are high amongst patients with CAP who survive the initial admission. This is primarily attributed to factors related to the aging population like the presence of multiple medical conditions and other health fragilities. [23] Most elderly CAP patients require special attention from health care professionals after discharge to reduce rehospitalization and mortality rates [24]. For this reason, the study analyzed factors associated with rehospitalization within 6 months and all-cause mortality (30 days and one year mortality) as secondary outcomes.

## 2. Materials and methods

Design and setting

Our study was conducted in the cantonal hospital of Baselland (KSBL), a district general hospital covering a stable population of 280 000 in Northwest Switzerland. We undertook a retrospective cohort study extracting all patients older than 18 years admitted to the hospital between January and December 2019 and categorized with an International Classification of Disease (ICD) code related to pneumonia (for more details see the ICD codes list in the appendix). A total of 573 patients were identified.

Inclusion and exclusion criteria

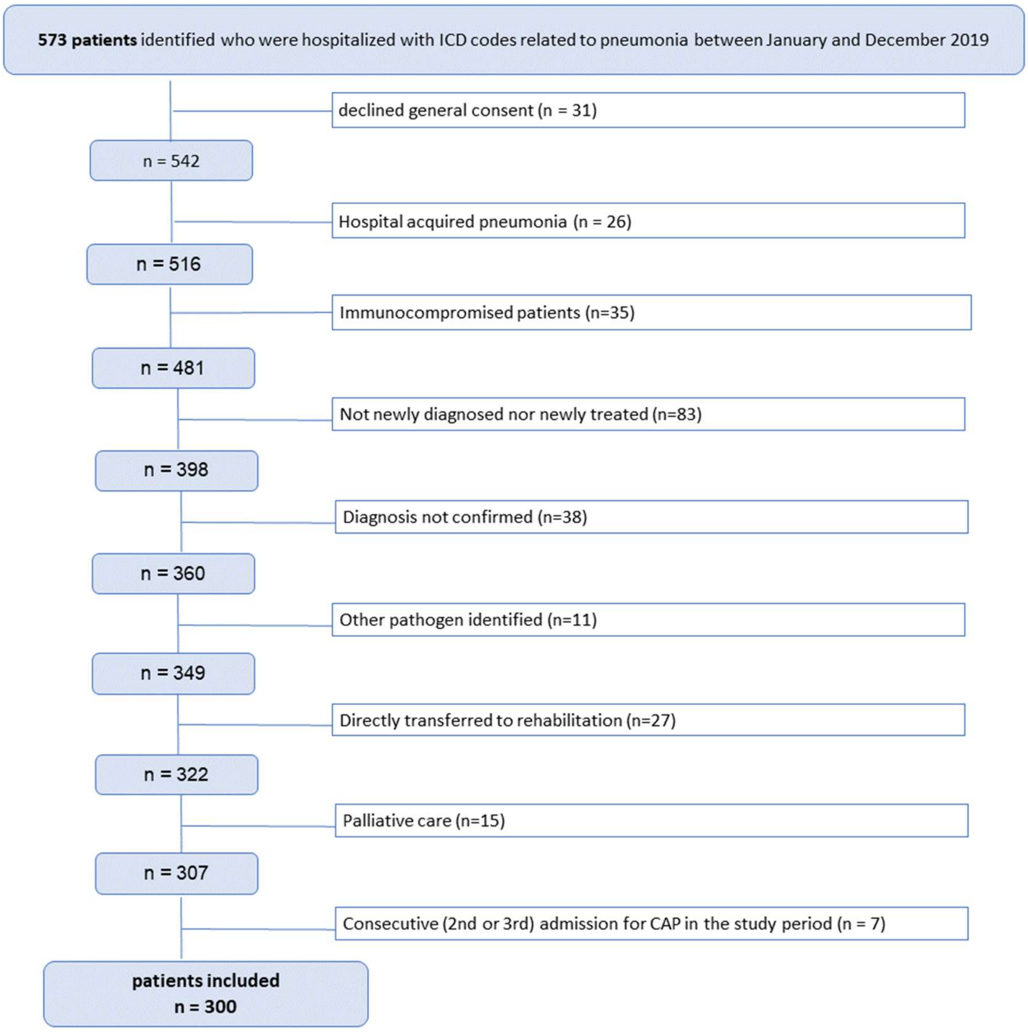
Cases were included in the study if a new CAP was the main reason for their hospitalization and their diagnosis was confirmed.

The following criteria were applied for exclusion:

- Denied research consent (n=31)
- Hospital acquired pneumonia (n=26)
- Immunocompromised patients (n=35)
- Patients with prior therapy prescribed by their general practitioner, not newly diagnosed nor newly treated (n=83)
- Diagnosis not confirmed (n=38)
- Directly transferred to rehabilitation (n=27)
- Palliative care (n=15)
- Other pathogens identified (n=11)
- Consecutive ($2^{nd}$ or $3^{rd}$) admission for CAP in the study period (n = 7)

After application of the eligibility criteria, data of 300 patients were included in the analysis (Figure 1).

**Figure 1:** Flowchart diagram for patient selection process




*Data Collection*

Basic data such as gender, age and LOHS were automatically extracted from the controlling system. The remaining variables were extracted manually by a study physician from the electronic patient record. To ensure the quality of the data, a subset was reviewed by a health scientist. The primary outcome of interest was LOHS. Additionally, secondary outcomes included rehospitalization within six months and all-cause mortality within 30 days and one year. To minimize the risk of bias, optimism, and overfitting, we did not perform data-driven selection of variables. Instead, potential predictors were selected based on the existing literature and clinical knowledge. Two researchers conducted a comprehensive literature review and consulted clinical experts in the field. Predictors for LOHS included variables available at the time of admission: demographic variables, vital signs, laboratory parameters, comorbidities, risk scores. "Indication for oxygen supplementation" was defined as the presence of at least one of the following conditions upon admission: oxygen saturation < 90%, oxygen supplementation already in place, respiratory rate >= 30. For the analysis of rehospitalization rate and mortality, events occurring during the hospitalization were also collected, such as oxygen supplementation during hospitalization and rehabilitation after discharge.

*Statistical analyses*

The outcome variables comprised LOHS (primary outcome), all-cause mortality (30 days and 1 year), and re-hospitalization within 6 months (secondary outcomes).

To minimize the risk of bias, optimism, and overfitting, no data-driven selection of variables was done. Assessed parameters included age, gender, housing situation before admission, type of pneumonia, medical history and vital signs measured at the time of admission, laboratory results, therapy and diagnostic work-up score. The analysis of LOHS was primarily on patients that were discharged alive, since only one patient died in-hospital a sensitivity analysis on the full data set was not necessary to perform.

For the outcome re- hospitalization, we further included the variable LOHS into the model, rehabilitation after discharge and oxygen supplementation during hospitalization.

We displayed measures of central tendency for descriptive statistics: mean and standard deviation (SD) if normally distributed and median with interquartile range if the distribution was skewed (determined by histogram assessment). For categorical variables we reported absolute and relative frequencies.

Variables with missing values up to 30% were imputed using the k-Nearest Neighbour algorithm (function knn.impute from the R package "bnstruct" [84,85]). A zero-truncated negative binomial regression was conducted to estimate the LOHS and its association with potential risk factors using the R package "VGAM". Logistic regression models were created to estimate the risk of death and rehospitalization, and its association with potential risk factors using the R package "stats".

All statistical analyses were performed using R, version 4.0.3 statistical software (R Foundation for Statistical Computing). All reported p-values were 2-sided; statistical significance was defined as $p < .05$.

## 3. Results

*Patient characteristics*

The patient characteristics are presented in Table 1. The median age at the time of hospital admission was 78.5 years and 53% were males. More than half of the patients had chronic cardiovascular comorbidities (58%), the second most frequent concomitant disease was COPD, followed by diabetes (29.7% and 18.3% respectively).

**Table 1:** Patient characteristics

| | all (n=300) | Missing n (%) |
|---|---|---|
| **Demographic** | | |
| Age at diagnosis, median [IQR] in years | 78.48 [67.56, 85.50] | -- |
| Gender (males), *n (%)* | 160 (53.3) | -- |
| **Vital Signs** | | |
| Respiratory rate at admission (median [IQR]) | 21.00 [18.00, 26.00] | 77 (25.7) |
| Indication for oxygen supplementation, n (%) | 102 (34.2) | 2 (0.7) |
| Oxygen supplementation during hospitalization, n (%) | 135 (45.2) | 1 (0.3) |
| Body temperature at admission (median [IQR]) | 37.60 [36.95, 38.40] | 9 (3.0) |
| Fever at admission, n (%) | 114 (38.9) | 7 (2.3) |
| Heart rate at admission (median [IQR]) | 91.00 [79.00, 104.00] | 1 (0.3) |
| Systolic blood pressure at admission (median [IQR]) | 132.00 [112.50, 147.00] | 1 (0.3) |
| Diastolic blood pressure at admission (median [IQR]) | 74.00 [65.00, 85.00] | 1 (0.3) |
| **Comorbidities** | | -- |
| Chronic cardiovascular, n (%) | 174 (58.0) | -- |
| Hypertension, n (%) | 177 (59.0%) | -- |
| Cancer, n (%) | 32 (10.7) | -- |
| Diabetes, n (%) | 55 (18.3%) | -- |
| Asthma, n (%) | 22 (7.3%) | -- |
| COPD, n (%) | 59 (19.7%) | -- |
| Other chronic respiratory diseases, n (%) | 42 (14.0) | -- |
| **Risk Scores** | | |
| GCS at admission (median [IQR]) | 15.00 [15.00, 15.00] | 7 (2.3) |
| qSOFA (median [IQR]) | 1.00 [0.00, 1.00] | 82 (27.3) |
| BMI (median [IQR]) | 26.00 [22.40, 30.25] | 137 (45.7) |

| | | |
|---|---|---|
| **Laboratory Values** | | |
| Leucocytes at admission (median [IQR]) | 11.90 [8.97, 15.00] | 0 |
| Procalcitonin at admission (median [IQR]) | 0.26 [0.10, 0.87] | 233 (77.7) |
| Atypic pneumonia diagnosed, n (%) | 19 (6.3) | 0 |
| **Discharge circumstances** | | |
| Rehabilitation, n (%) | 51 (16.6) | -- |
| Discharged home, n (%) | 217 (72.3) | -- |
| Discharged to a care facility, n (%) | | |
| **Outcomes** | | |
| LOHS (median [IQR]) | 7.00 [5.00, 9.00] | -- |
| Rehospitalization within six months, n (%) | 97 (31.6%) | -- |
| In-hospital death, n (%) | 1 (0.3) | -- |
| 30-days death, n (%) | 8 (2.7) | -- |
| One year death, n (%) | 35 (11.7) | -- |

*Prediction of LOHS, rehospitalization and mortality*

Our primary aim was to examine factors associated with LOHS. Table 2 provides coefficient estimates for predictors of LOHS in patients who did not die. Regression coefficients are shown as incident risk ratio (IRR). The median LOHS of the overall cohort was 7 days. The analysis of the prediction model for LOHS identified four statistically significant predictors: sex, age, qSOFA score and atypical pneumonia.

The LOHS prediction at the intercept (7.5 days) is the LOHS when all covariates are at 0 (for categorical covariates) or at their mean (for continuous covariates). The predicted LOHS of the model for each variable is presented for 1 unit increase. A higher increase occurs when the qSOFA score increases by 1 unit the predicted LOHS rise to 8.5 days. Women tended to stay one night longer than men, while people with atypical pneumonia compared to those without tended to stay 3 nights longer, assuming all other variables are held constant.

**Table 2.** Results of multivariable zero-truncated negative binomial regression model for length of hospital stay (LOHS) estimation in CAP patients who survived the first hospital admission (n =299).

| | LOHS prediction | IRR | (95%CI) | | p-value |
|---|---|---|---|---|---|
| (Intercept) | 7.458 | 11.947 | 1.18 | 121.0 | 0.036 |
| **Gender (males)** | **6.562** | **0.877** | **0.776** | **0.992** | **0.036** |
| **Age** | **7.511** | **1.007** | **1.002** | **1.012** | **0.003** |
| Chronic cardiovascular | 8.217 | 1.103 | 0.957 | 1.273 | 0.176 |
| COPD | 7.126 | 0.955 | 0.822 | 1.108 | 0.542 |
| Asthma | 6.654 | 0.89 | 0.708 | 1.119 | 0.318 |
| Diabetes | 7.148 | 0.958 | 0.821 | 1.118 | 0.583 |
| Active cancer | 8.12 | 1.09 | 0.905 | 1.314 | 0.364 |
| **qSOFA** | **8.508** | **1.143** | **1.049** | **1.246** | **0.002** |
| Heart rate at admission | 7.472 | 1.002 | 0.999 | 1.005 | 0.218 |
| Body temperature at admission | 7.207 | 0.966 | 0.909 | 1.026 | 0.26 |
| CRP at admission | 7.459 | 1 | 1 | 1.001 | 0.631 |
| Leucocytes at admission | 7.46 | 1 | 0.993 | 1.008 | 0.936 |
| **Atypic pneumonia diagnosed** | **10.088** | **1.357** | **1.012** | **1.819** | **0.041** |

Our secondary aims included the analyses of factors associated with rehospitalization and mortality.

The results for our secondary outcome concerning rehospitalization rate are reported in table 3. The odds for rehospitalization within 6 months in KSBL were also significantly higher for patients with a higher qSOFA score at admission. Moreover, patients with diabetes and those who were admitted to rehabilitation had a higher chance of being rehospitalized within 6 months. No other variable was found to be significantly associated with rehospitalization.

**Table 3.** Results of multivariable logistic regression model for rehospitalization within 6 months in patients with CAP

| | 0R | (95%CI) | | p-value |
|---|---|---|---|---|
| Gender (males) | 0.964 | 0.549 | 1.693 | 0.898 |
| age | 1.016 | 0.994 | 1.039 | 0.164 |
| Chronic cardiovascular | 1.123 | 0.582 | 2.177 | 0.73 |
| COPD | 1.021 | 0.504 | 2.016 | 0.954 |
| asthma | 1.759 | 0.622 | 4.718 | 0.269 |
| **diabetes** | **2.149** | **1.104** | **4.172** | **0.024** |
| Active cancer | 1.565 | 0.682 | 3.557 | 0.284 |
| **qSOFA** | **1.958** | **1.295** | **3.002** | **0.002** |
| Oxygen during hospitalization | 0.636 | 0.357 | 1.116 | 0.118 |
| LOHS | 1.055 | 0.984 | 1.132 | 0.134 |
| **Rehabilitation after discharge** | **2.222** | **1.017** | **4.855** | **0.044** |

The results of the multivariable logistic regression models for mortality are displayed in table 4 (30 days mortality) and table 5 (1 year mortality).

In both predictive models age and an active cancer diagnosis were the only two significant variables associated with mortality. No other variable was found to be significantly associated with mortality.

**Table 4:** Results of multivariable logistic regression model for 30 days mortality in patients with CAP

| | **0R** | **(95%CI)** | | **p-value** |
|---|---|---|---|---|
| Gender (males) | 13.219 | 1.235 | 483.529 | 0.075 |
| **age** | **1.248** | **1.056** | **1.562** | **0.026** |
| Chronic cardiovascular | 0.953 | 0.078 | 25.315 | 0.972 |
| COPD | 0.335 | 0.012 | 3.534 | 0.419 |
| asthma | 0 | | 5.82043E+66 | 0.993 |
| diabetes | 0.956 | 0.059 | 9.993 | 0.971 |
| **Active cancer** | **32.671** | **4.787** | **369.134** | **0.001** |
| qSOFA | 0.817 | 0.198 | 3.135 | 0.768 |
| Oxygen during hospitalization | 6.787 | 0.864 | 101.466 | 0.103 |
| LOHS | 1.144 | 0.909 | 1.447 | 0.246 |
| Rehabilitation after discharge | 0.259 | 0.01 | 3.353 | 0.356 |

**Table 5:** Results of multivariable logistic regression model for one year mortality in patients with CAP

| | **0R** | **(95%CI)** | | **p-value** |
|---|---|---|---|---|
| Gender (males) | 1.352 | 0.594 | 3.166 | 0.477 |
| **age** | **1.073** | **1.025** | **1.132** | **0.005** |
| Chronic cardiovascular | 1.53 | 0.563 | 4.684 | 0.425 |
| COPD | 0.722 | 0.247 | 1.881 | 0.525 |
| asthma | 0.773 | 0.106 | 3.445 | 0.763 |
| diabetes | 1.847 | 0.725 | 4.518 | 0.185 |
| **Active cancer** | **4.408** | **1.68** | **11.427** | **0.002** |
| qSOFA | 1.194 | 0.665 | 2.126 | 0.547 |
| Oxygen during hospitalization | 1.6 | 0.714 | 3.657 | 0.256 |
| LOHS | 1.025 | 0.922 | 1.13 | 0.63 |
| Rehabilitation after discharge | 1.234 | 0.401 | 3.541 | 0.703 |

## 4. Discussion

This retrospective observational cohort study of patients with CAP showed that LOHS is influenced by demographic factors such as older age and female gender and by disease specific factors like qSOFA score and atypical pneumonia. Other factors such as other types of comorbidities, vital signs (other than included in the qSOFA) and laboratory values at admission were not associated with longer LOHS.

Interestingly our results show that women had a worse outcome compared to men. Gender differences have been observed in the clinical course and outcomes of people with CAP and historically men have been found to have worse outcomes, particularly in terms of short- and long-term mortality. [27,28] Although little evidence  in terms of LOHS is available, our results are consistent with the international multicenter study by the Community Acquired Pneumonia Organization that followed patients for 10 years. In this study Arnold and colleagues found that women had significantly longer LOHS and also worse outcomes in terms of time to clinical stability and mortality within 28 days. [29] Gender differences clearly warrant further confirmation and validation because causal inference cannot be drawn. However, if confirmed in future, the current concept that female patients have a lower risk than males with CAP may need to be revised and current scoring system adjusted (for example subtraction of 10 points for females in the Pneumonia Severity Index - PSI).

The quick Sequential (Sepsis-related) Organ Failure Assessment (qSOFA) score is another severity assessment tool and validated prognostic model devised by Seymour et al. [30,31] Originally it was developed to predict sepsis using three main clinical criteria, namely altered mental status, low systolic blood pressure and high respiratory rate. In line with other studies, our results also confirm the prognostic validity of the qSOFA score in predicting the length of hospital stay. [30,32–34] The role of qSOFA in LOHS was confirmed recently by Koch et al. [35], however the impact of the single items composing the score was unclear. For this reason, in our study, we also analyzed the items of the qSOFA score separately and we found that altered mental status (GCS < 15) and blood pressure (Systolic BP ≤100) were significantly predictive for LOHS (for more details see Table A1 in the appendix). The main advantage of implementing the qSOFA score is that it does not require laboratory tests and allows for rapid and repetitive assessment. In addition to the task force’s recommendation to use the qSOFA tool to further investigate potential organ dysfunction, or to initiate or escalate appropriate therapy, our results suggest that the qSOFA score can be integrated in predictive models as a risk predictor for extended LOHS.

Another point worth discussing is the fact that atypical pneumonia was predictive for extended LOHS. In community-acquired pneumonia examples of typical pathogens are streptococcus pneumoniae, haemophilus influenzae, and atypical pathogens are mycoplasma pneumoniae, chlamydia pneumoniae and staphylococcus aureus. [36] Atypical pneumonia often expresses more unspecific symptoms such as headache, low fever, dyspnea, dry cough and only slightly elevated inflammatory biomarkers; moreover, the clinical presentation can range from mild symptoms to severe illness with respiratory failure or sepsis. [37] Approximately 7% to 20% of cases of community-acquired pneumonia are believed to be caused by atypical bacterial microorganisms, which cannot be detected through gram stain and pose challenges in terms of culturing. [38] Moreover, the presence of atypical pathogens in some patients with community-acquired pneumonia (CAP) poses a challenge in the selection of empirical antibiotic treatment. These pathogens are inherently resistant to beta-lactam drugs, which are commonly used as the initial antibiotic treatment. [39] The dilemma arises from the fact that adding antibiotic coverage specifically for atypical pathogens might carry the risk of adverse effects and promotes the development of antimicrobial resistance. [40] On the other hand, withholding such coverage may potentially worsen the prognosis if an atypical pathogen is indeed the causative agent of the pneumonia. [41,42] Therefore, in our study, we also considered the presence of atypical pathogens as a potential predictor when examining the length of stay in patients with CAP. We recognized that the use or omission of antibiotic coverage for atypical pathogens could influence the clinical course and outcomes, including the LOHS. Hence, the observed association between atypical pneumonia and an extended length of stay in our study could potentially be attributed to the challenges involved in treatment. Specifically, the addition of antibiotic treatment coverage to address atypical pathogens might inadvertently lead to adverse effects, thereby prolonging the hospitalization period. Alternatively, the diagnostic tests employed to identify atypical pathogens may require additional time, contributing to the longer length of stay.

Our secondary outcomes included rehospitalization in KSBL within 6 months. We detected that in our study population rehospitalization within 6 months was significantly associated with factors such as diabetes, qSOFA score and rehabilitation after discharge. The percentage of patients who were rehospitalized within 6 months was 31.6%, which is similar to the ranges of two non-recent studies where the assessed cumulative readmission rates were 22 and 35.6%. [43,44] In term of readmission rate in fact is not common to assess long term outcome as stated by Prescott in a systematic review, the majority of published literature concentrate their focus on 30-days readmission and the percentage variates from a minimum of 16.8 to a maximum of 20.1%. [45] The most recent study published in 2021 by Averin et al.

assessing late readmission following hospitalization for pneumonia among American adults analyzed one year readmission and the proportion reached 42.3% of the study population. [46]

As previously mentioned the qSOFA score is a validated prognostic tool for sepsis, a recent study investigated the prognostic performance of qSOFA for in-hospital mortality and ICU admission [47], but its accuracy in predicting long term outcome in terms of rehospitalization within 6 months has not been established.

Interestingly diabetes was the only chronic health condition associated with rehospitalization within 6 months. Previous studies have found a relationship between diabetes and CAP incidence [48] or hospitalization rate [49] or demonstrated that patients with diabetes have worse discharge outcome compared to patients without diabetes. [50] A recent published systematic review and meta-analysis by Fang et al. found that diabetes mellitus was significantly associated with the hospital readmission rate among pneumonia patients (pooled OR = 1.18; 95%CI: 1.08-1.28) [24], which is confirmed by our results. So, despite advances in treatments, diabetes is still associated with a higher risk of adverse outcomes and healthcare providers should take this finding into account. Although CAP patients who also suffer from diabetes are at elevated risk for adverse events and a complicated clinical course as explained above, further studies are required in order to clarify the underlying mechanisms and impact of disrupted glucose metabolism on the development and clinical outcome of CAP in light of rehospitalization rates.

It is worth mentioning that discharge to rehabilitation was found to be significantly associated with rehospitalization. Patients who were sent to rehabilitation after discharge had a higher chance of being readmitted to the hospital within 6 months compared to those who did not attend rehabilitation. This finding contradicts the initial hypothesis that rehabilitation would reduce the risk of rehospitalization. Possible explanations may include the complexity and severity of the underlying conditions requiring rehabilitation, the intensity or duration of the rehabilitation program, or other unmeasured factors that could influence the outcomes.

In order to further investigate underlying reasons for the positive relationship between rehabilitation and rehospitalization we conducted a post hoc analysis comparing the characteristics of patients being rehabilitated after hospitalization with those not being rehabilitated. As displayed in table B in the appendix, significant differences were detected. The age of patients who received rehabilitation was significantly higher compared to those who did not (median 82.73 and 77.35 respectively; p-value 0.004). Similarly, patients who underwent rehabilitation had a significantly longer LOHS (median 11 days and 6 respectively 6.00; p-value 0.001). Other factors, such as chronic cardiovascular disease, COPD, respiratory insufficiency, parapneumonic effusion, and cardiovascular complications, also showed significant differences between the two groups. The detected significant differences between the two groups in terms of age, comorbidity burden, and hospital complications might explain the positive association between rehabilitation and rehospitalization. Hence, it is necessary to carefully interpret the association between rehabilitation and rehospitalization, considering the confounding effects of these patient characteristics.

Moreover, a previous study has shown promising results especially in the short-term, specifically focusing on the 30-day hospital readmission rate. [51] The majority of the studies investigating the positive effects of rehabilitation mainly focused on different outcomes. [52–55] It is important to note that our study differs from these previous investigations as we examined rehospitalization rates within a longer time frame of six months. This extended duration allows us to capture readmissions that may occur beyond the initial 30-day period and provides a more comprehensive understanding of the factors influencing rehospitalization. Further exploration is needed to better understand this unexpected association.

In terms of mortality, we observed that the in-hospital mortality was very low, only one patient died during the initial hospitalization as displayed in Table 1. This can be explained by the fact that all patients who were transferred for palliative care or directly sent to another hospital were excluded from the study. On the contrary, we noticed that almost one quarter of the overall mortality within one year happened within 30-days after discharge (22.9%).

This trend is also confirmed by Wadhera in a study with population-based data of almost 16300 patients conducted in Germany. The research revealed a significant increase in mortality over time, with a 4.7% rise between in-hospital mortality (17.2%) and 30-day mortality (21.9%). [56] Similarly, a study conducted in the United States with a 10-year cohort of about 3 million CAP patients reported a high 30-day post-discharge mortality of 8.2%. [57]

Both multivariable logistic models for 30-day- and 1-year mortality revealed that age and cancer diagnosis were associated with higher risk of mortality. The findings from our study reinforce prior observations that all-cause mortality during the year subsequent to hospital admission for pneumonia is linked to increasing age and worsening comorbidity profile. [46,58,59]

A recent study concluded that while long-term mortality following CAP was primarily associated with comorbidities, there is potential for early post-discharge complications (within 30 days) to be attributed to CAP-related issues that may benefit from targeted interventions [60]. However, our results did not find different predictors between the two mortality outcomes.

Finally, it is important to note that LOHS was not significantly associated with mortality nor rehospitalization, implying that a shorter LOHS did not show an increased risk of readmission or post-discharge mortality.

Strengths, limitations, and further research

The novelty of our study lies in its comprehensive encompassing of three important quality indicators as research outcomes (LOHS, rehospitalization and mortality). The prediction models included various factors such as demographic variables, health-related variables, and laboratory values available at the time of admission. A further strength of our research was the possibility to investigate long-term outcomes such as mortality within one year, as this data was available for all patients. However, there are certain limitations to consider. As a retrospective study, the quality of the data depended on accurate documentation in the patient files, which may have resulted in incomplete information.

Furthermore, information on rehospitalization within six months was limited to a specific hospital due to privacy policies, potentially missing readmissions to other healthcare facilities. However, - according to a previous study - in Switzerland, most unplanned readmissions occur within the same hospital. [61]

Overall, our study provides a foundation for future research and contributes valuable insights into other aspects of CAP, particularly focusing on possible predictors of LOHS, mortality and rehospitalization, available at admission time. The identification of predictors available at the time of admission might help to promptly identify patients at higher risk of adverse outcomes and allow healthcare providers to prioritize their care, allocate appropriate resources, and develop personalized management strategies tailored to patients` specific needs.

Further studies are needed to investigate the underlying causes contributing to the association between atypical pneumonia and LOHS. As mentioned before, predictive models could include data regarding antibiotic coverage and time until atypical pneumonia was diagnosed. By conducting additional research, a more comprehensive understanding can be obtained, and targeted interventions to optimize patient care and reduce the burden associated with prolonged hospital stays could be developed.

## 5. Conclusion

Understanding the factors that are associated with LOHS in patients with CAP has clinical implications and may help healthcare providers to deliver efficient care and to allocate adequate resources in the management of these patients. In summary, the results of this study showed that female sex, advanced age, higher qSOFA score and atypical pneumonia were predictive for longer LOHS. Diabetes, high qSOFA and discharge to rehabilitation were associated with a higher chance of rehospitalization within 6 months, whereas mortality within 30-days and within one year were both linked to advanced age and the presence of an active cancer diagnosis. Moreover, our study confirmed the important role of qSOFA, not only as a predictive tool for sepsis but also for LOHS and rehospitalization in patients with CAP.

## 6. Appendix

List of ICD-10 Codes used for patients' selection in detail:

- A 48.1 Pneumonic legionnaires disease
- J 10.0 Influenza due to other identified influenza virus with unspecified type of pneumonia
- J 12.0 Adenoviral pneumonia
- J 12.1 Respiratory syncytial virus pneumonia
- J 12.2 Parainfluenza virus pneumonia
- J 12.3 Human metapneumovirus pneumonia
- J 12.8 Other viral pneumonia
- J 12.9 Viral pneumonia, unspecified
- J 13 Pneumonia due to Streptococcus pneumoniae
- J 14 Pneumonia due to Hemophilus influenzae
- J. 15.1 Pneumonia due to Pseudomonas
- J 15.2 Pneumonia due to Staphylococcus
- J 15.3 Pneumonia due to streptococcus, group B
- J 15.4 Pneumonia due to other streptococci
- J 15.5 Pneumonia due to Escherichia coli
- J 15.6 Pneumonia due to other aerobic Gram-negative bacteria
- J 15.7 Pneumonia due to Mycoplasma pneumoniae
- J 15.8 Other bacterial pneumonia
- J 15.9 Unspecified bacterial pneumonia
- J 16.0 Chlamydial pneumonia
- J 16.8 Pneumonia due to other specified infectious organisms
- J 18.0-Bronchopneumonia, unspecified organism
- J 18.1 Lobar pneumonia, unspecified organism
- J 18.8 Other pneumonia, unspecified organism
- J 18.9 Pneumonia, unspecified organism
- J 85.1 Abscess of lung with pneumonia

*Supplemental Tables*

**Table A:** Multivariable zero-truncated negative binomial regression model for LOHS estimation in CAP survivors qSOFA items separately assessed (n = 299).

| | **LOHS prediction** | **IRR** | **(95%CI)** | | **p-value** |
|---|---|---|---|---|---|
| (Intercept) | 6.693 | | | | |
| **Gender (males)** | **5.883** | **0.875** | **0.775** | **0.989** | **0.032** |
| **age** | **6.738** | **1.007** | **1.002** | **1.012** | **0.005** |
| chronic cardiovascular | 7.455 | 1.117 | 0.97 | 1.285 | 0.124 |
| COPD | 6.455 | 0.964 | 0.831 | 1.117 | 0.623 |
| asthma | 5.96 | 0.887 | 0.708 | 1.112 | 0.299 |
| diabetes | 6.49 | 0.969 | 0.83 | 1.131 | 0.689 |
| active cancer | 7.463 | 1.118 | 0.928 | 1.347 | 0.241 |
| **Altered mental status (GSC <15)** | **8.234** | **1.235** | **1.079** | **1.414** | **0.002** |
| **Systolic BP ≤100** | **8.646** | **1.297** | **1.064** | **1.582** | **0.010** |
| Respiratory rate ≥22 | 7.142 | 1.069 | 0.947 | 1.206 | 0.282 |
| Heart rate at admission | 6.708 | 1.002 | 0.999 | 1.006 | 0.131 |
| Body temperature at admission | 6.478 | 0.967 | 0.911 | 1.027 | 0.274 |
| CRP at admission | 6.694 | 1 | 1 | 1.001 | 0.458 |
| Leucocytes at admission | 6.696 | 1.001 | 0.993 | 1.008 | 0.877 |
| **Atypic pneumonia diagnosed** | **9.251** | **1.389** | **1.039** | **1.856** | **0.026** |

**Table B:** Post-hoc analysis. Comparison between patients undergoing rehabilitation after hospitalization and those not being rehabilitated.

| Variables | Overall (n=300) | Rehabilitation (no) n=253 | Rehabilitation (yes) n=47 | p-value | Missing |
|---|---|---|---|---|---|
| **age (median [IQR])** | **78.48 [67.56, 85.50]** | **77.35 [66.23, 84.66]** | **82.73 [78.04, 88.55]** | **0.004** | **0** |
| **LOHS (median [IQR])** | **7.00 [5.00, 9.00]** | **6.00 [5.00, 8.00]** | **11.00 [7.50, 14.50]** | **<0.001** | **0** |
| BMI (median [IQR]) | 26.00 [22.40, 30.25] | 26.50 [22.85, 30.37] | 25.00 [21.00, 27.30] | 0.085 | 45.7 |
| **Oxygen during hospitalization in days (median [IQR])** | **1.00 [0.00, 3.00]** | **1.00 [0.00, 3.00]** | **3.50 [1.00, 6.75]** | **0.001** | **26.3** |
| qSOFA (median [IQR]) | 1.00 [0.00, 1.00] | 1.00 [0.00, 1.00] | 1.00 [0.00, 1.00] | 0.265 | 27.3 |
| Gender (male), n (%) | 160 (53.3) | 138 (54.5) | 22 (46.8) | 0.414 | 0 |
| Atypic pneumonia diagnosed, n (%) | 12 (4.0) | 10 (4.0) | 2 (4.3) | 1 | 0 |
| **Chronic cardiovascular disease, n (%)** | **174 (58.0)** | **140 (55.3)** | **34 (72.3)** | **0.045** | **0** |
| Diabetes, n (%) | 55 (18.3) | 49 (19.4) | 6 (12.8) | 0.385 | 0 |
| **COPD, n (%)** | **59 (19.7)** | **44 (17.4)** | **15 (31.9)** | **0.036** | **0** |
| Asthma, n (%) | 22 (7.3) | 21 (8.3) | 1 (2.1) | 0.236 | 0 |
| Other chronic respiratory disease, n (%) | 42 (14.0) | 31 (12.3) | 11 (23.4) | 0.073 | 0 |
| Active cancer, n (%) | 32 (10.7) | 24 (9.5) | 8 (17.0) | 0.201 | 0 |
| Severe immunosuppression, n (%) | 2 (0.7) | 1 (0.4) | 1 (2.1) | 0.716 | 0 |
| Care facility resident, n (%) | 50 (16.7) | 46 (18.2) | 4 (8.5) | 0.155 | 0 |
| **Oxygen during hospitalization**, n (%) | **135 (45.2)** | **106 (42.1)** | **29 (61.7)** | **0.02** | **0.3** |
| Admission to ICU, n (%) | 27 (9.0) | 20 (7.9) | 7 (14.9) | 0.208 | 0 |
| ARDS, n (%) | 300 (100.0) | 253 (100.0) | 47 (100.0) | NA | 0 |
| Sepsis, n (%) | 6 (2.0) | 4 (1.6) | 2 (4.3) | 0.525 | 0 |
| **Respiratory insufficiency**, n (%) | **25 (8.3)** | **15 (5.9)** | **10 (21.3)** | **0.001** | **0** |
| **Cardiovascular complications, n (%)** | **42 (14.0)** | **29 (11.5)** | **13 (27.7)** | **0.007** | **0** |
| Acute kidney injury, n (%) | 54 (18.0) | 45 (17.8) | 9 (19.1) | 0.987 | 0 |
| Anemia, n (%) | 19 (6.4) | 19 (7.6) | 0 (0.0) | 0.109 | 1 |
| **Parapneumonic effusion, n (%)** | **34 (11.3)** | **22 (8.7)** | **12 (25.5)** | **0.002** | **0** |
| Syncope, n (%) | 3 (1.0) | 3 (1.2) | 0 (0.0) | 1 | 0 |
| In-hospital fall, n (%) | 22 (7.4) | 16 (6.3) | 6 (12.8) | 0.214 | 0.3 |
| Elevated liver parameters, n (%) | 23 (7.7) | 21 (8.3) | 2 (4.3) | 0.51 | 0 |
| Neurological complications, n (%) | 14 (4.7) | 9 (3.6) | 5 (10.6) | 0.082 | 0 |
| Gastrointestinal complications, n (%) | 14 (4.7) | 12 (4.7) | 2 (4.3) | 1 | 0 |
| Electrolyte disorder, n (%) | 53 (17.7) | 44 (17.4) | 9 (19.1) | 0.935 | 0 |

**Statement of Ethics**

The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association. This study protocol was reviewed and approved by the ethics committee of northwest and central Switzerland (Project-ID 2021-00964).

**Conflict of Interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Author Contributions**

G. Lüthi-Corridori and Andrea Roth were responsible for data collection. G. Lüthi-Corridori, S. Giezendanner and M. Boesing were responsible for data analysis. G. Lüthi-Corridori M. Boesing and J.D. Leuppi were responsible for designing the study. All authors contributed to writing the manuscript and agreed to be accountable for the content of the work.

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**Data Availability Statement**

All data generated were analyzed during this study and the results included in this article. Further inquiries can be directed to the corresponding author.

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# CHAPTER IV

## Predictors of length of stay, rehospitalization and mortality in COPD patients: a retrospective cohort study

# Predictors of length of stay, mortality and rehospitalization in COPD patients: a retrospective cohort study

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**Abstract**

Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic lung disease that has a significant impact on individuals and healthcare systems worldwide. This study aimed to identify factors that predict the length of hospital stay (LOHS), one-year mortality and rehospitalization within 6 months in patients admitted for acute exacerbation of COPD (AECOPD). A retrospective cohort study was conducted using data from 170 patients admitted to a district general hospital in Switzerland between January 2019 and February 2020. Sociodemographic and health-related variables measured at admission were analyzed as potential predictors. Multivariable zero-truncated negative binomial and logistic regression analyses were performed to assess risk factors for LOHS (primary endpoint), mortality and re-hospitalization. The results showed that indication for oxygen supplementation was the only significant predictor of LOHS. In the logistic regression analysis, older age, COPD severity stages GOLD III and IV, active cancer and arrhythmias were associated with higher mortality, whereas rehabilitation after discharge was associated with lower mortality. There were no significant associations regarding rehospitalization. This study identified routinely available predictors for LOHS and mortality, which may further advance our understanding of AECOPD and thereby improve patient management, discharge planning, and hospital costs. The protective effect of rehabilitation after hospitalization regarding lower mortality warrants further confirmation and may improve the comprehensive management of patients with AECOPD.

## 1. Introduction

Chronic obstructive pulmonary disease (COPD) is “a common preventable and treatable chronic lung disease” that is the third leading cause of death worldwide. [1] In Switzerland, approximately 400.000 people suffer from COPD. [2] COPD imposes a significant medical and financial strain on patients and healthcare systems, resulting in di-minished quality of life, reduced life expectancy, and substantial healthcare expenditures globally. [3,4]

In addition, COPD patients often are affected by other life-challenging comorbidities such as ischemic heart disease, osteoporosis, musculoskeletal disorders, lung cancer, de-pression or anxiety. [5] Acute Exacerbation of COPD (AECOPD) refers to a worsening of COPD symptoms, including increased dyspnea, cough, sputum production and sputum purulence. [6] AECOPD are often triggered by infections, leading to deterioration in lung function and necessitating changes in treatment, hospital admission, or intensive care. [7,8] The frequency of previous exacerbations is a strong predictor of future exacerbations, and managing and preventing exacerbations are crucial in improving patient quality of life and reducing the negative impact on the disease's progression and mortality. [6,8–10]

Together with exacerbations of COPD, comorbidities contribute to the overall severity in individual patients and influence the disease progression and prognosis unfavorably. [3] An exacerbation of COPD frequently leads to hospital admission and, COPD patients tend to have prolonged hospital stays, therefore requiring a large number of medical, clinical and financial resources. [4–6] When already having had an exacerbation, pronounced dyspnea and cerebrovascular insult are significantly associated with re-exacerbation. [7]

The length of hospital stay (LOHS) in patients with AECOPD can be influenced by various factors, including sociodemographic [8], health-related characteristics [9], and hospital care-related features [10], as reported by previous studies. Literature has shown that common factors associated with prolonged hospitalization include older age, comorbidities, and socioeconomic deprivation. [8–14] Older patients may experience slower recovery, while the presence of comorbid conditions can complicate management, both con-tributing to extended stays. Moreover, socioeconomically deprived patients may face barriers to accessing healthcare and post-acute care services, further prolonging hospitalization. [8] Similarly, the presence of comorbidities for example cardiovascular diseases, cancer or diabetes, can complicate the management of AECOPD and necessitate more comprehensive treatment plans, which might consequently extend LOHS. In terms of se-verity of AECOPD patients with more severe exacerbations necessitating intensive interventions require also longer recovery periods. [12,13] Additionally, patients with a history of frequent hospitalizations for AECOPD may have more advanced disease and increased susceptibility to recurrent exacerbations, necessitating longer hospital stays for comprehensive treatment and recovery. [9,14] The availability of specialized respiratory care units, access to early interventions such as non-invasive ventilation, and timely access to medical resources can impact the course of treatment and potentially shorten the hospital stay. [10]. Moreover, the availability and coordination of post-discharge care services, such as pulmonary rehabilitation or home care, are crucial factors affecting the hospital stay duration. Efficient discharge planning and access to post-discharge care services can help reduce hospital stays. [14]

However, due to the wide range of influencing factors, there is currently no standardized approach for predicting LOHS in patients with AECOPD. The primary objective of this study was to identify factors that might predict LOHS in patients admitted for AECOPD. By identifying patient characteristics that influence LOHS, decision-makers can better plan hospital management strategies. Specifically, we retrospectively investigated whether commonly available sociodemographic and health-related variables measured at admission were associated with the primary outcome LOHS. The study also aimed to establish a prediction model for length of stay for patients hospitalized with AECOPD. While reducing LOHS may decrease hospital costs, it could also negatively affect the qual-ity of care. Therefore, we also examined factors associated with all-cause mortality within one year and rehospitalization within 6 months as secondary outcomes. Early prediction of LOHS using variables measured at admission could potentially improve patient management, facilitate optimal discharge planning, shorten LOHS, and ultimately reduce hospital costs.

## 2. Materials and Methods

### 2.1 Study design

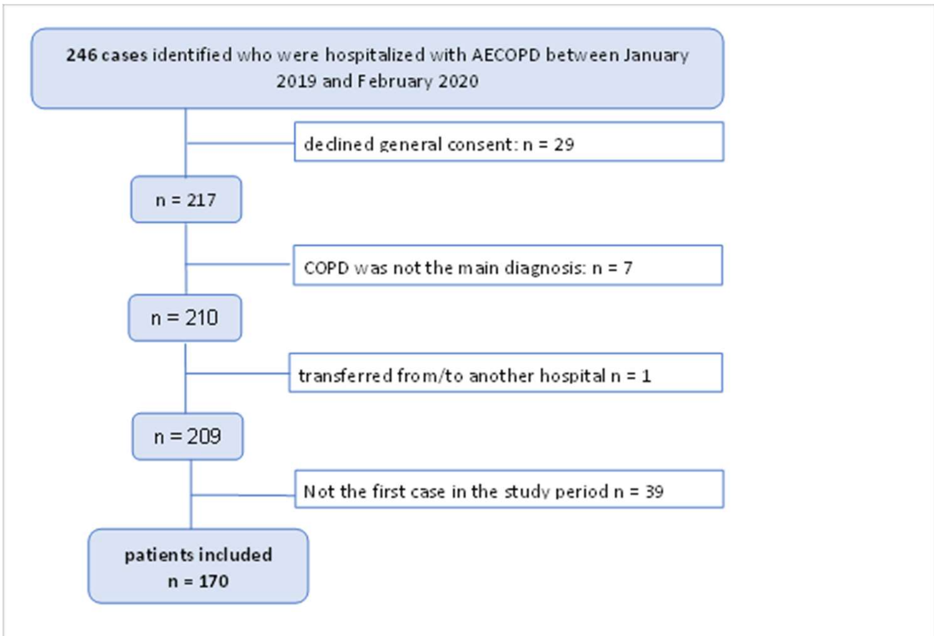
This retrospective observational study was performed using existing data of patients presenting with AECOPD exacerbations at the emergency departments of the cantonal hospital of Baselland (KSBL), a district university teaching hospital covering a stable population of a quarter million in Northwest Switzerland. [13] We undertook a retrospective cohort study between January 2019 and February 2020. A total of 246 patients were identified who presented at the emergency departments with acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

### 2.2. Inclusion and exclusion criteria

Data from the electronic records of these patients was individually reviewed. Cases were included if the patients were older than 18 years, were admitted via the emergency room (ER), did not have a documented refusal of the hospital`s general consent and had a confirmed diagnosis of COPD exacerbation as their main diagnosis. (For more information see “Informed Consent Statement”)

After the application of the eligibility criteria 170 patients were included in the analysis. (Figure 1)

Figure 1. Flowchart diagram for patient selection process




### 2.3. Data collection

The primary outcome of interest was LOHS. Additionally, secondary outcomes included all-cause mortality within one year and rehospitalization within six months. To minimize the risk of bias, optimism, and overfitting, we did not perform data-driven se-lection of variables. Instead, potential predictors were selected based on the existing literature and clinical knowledge. Two researchers conducted a comprehensive literature re-view and consulted clinical experts in the field. Predictors for LOHS included variables available at the time of admission: demographic variables (age, gender), vital signs (indication for oxygen supplementation), comorbidities (cardiovascular diseases, active cancer, asthma overlapping and diabetes), COPD severity (GOLD status I, II, III, IV), laboratory data (CRP, leukocytosis, eosinophil count) and admission urgency (ambulance transportation). The variable indication for oxygen supplementation was defined as both cases where oxygen saturation was below 90% and cases where oxygen supplementation was given at admission. For the analysis of rehospitalization rate and mortality, events occurring during the hospitalization were also included, such as LOHS and discharge destination (rehabilitation).

Study data was collected manually searching in all available electronic patient records and managed using REDCap electronic data capture tools hosted at the Cantonal Hospital of Baselland. [16] The collection was performed by a doctor and a random sample of the data was checked by a health scientist.

*2.4 Data analysis*

The primary analysis of LOHS was performed on the group of patients that were discharged alive, a sensitivity analysis was performed on the full data set. For descriptive statistics, different measures of central tendency were used based on the distribution of the data: mean and standard deviation (SD) were displayed for normally distributed variables, while median and interquartile range (IQR) were reported for skewed variables, which were identified through histogram analysis. Analyzing age as a continuous variable allows us to capture the linear relationship between age and mortality risk, which can provide valuable insights into the gradual increase in mortality risk with advancing age. (see Figure 1A in the appendix). For categorical variables, we presented absolute and relative frequencies. Variables with missing values were imputed using the k-Nearest neighbor algorithm (function knn.impute from the R-package "bnstruct") [17]. A zero-truncated negative binomial regression was conducted to estimate the LOHS and its association with potential risk factors using the R package "VGAM." Logistic regression models were created to estimate the risk of death and rehospitalization, and its association with potential risk factors. As a sensitivity analysis, all regression models were additionally performed on the original, non-imputed data set. All statistical analyses were performed using R, version 4.0.3 statistical software. [18] All p-values reported were 2-sided; statistical significance was defined as $p < 0.05$.

## 3. Results

### *3.1 Patient characteristics*

A total of 246 cases were identified. After the application of inclusion and exclusion criteria, 170 patients were included in the analysis (Figure 1). Table 1 presents the patient characteristics of 170 patients, along with the percentage of missing data.

Table 1. Patient characteristics

| | **all (n=170)** | **Missing (%)** |
|---|---|---|
| **Demographic** | | |
| Age at diagnosis, median [IQR] in years | 75 [68-79] | -- |
| Gender (Male), n (%) | 91 (53.5 %) | -- |
| **Vital Signs** | | |
| Indication for oxygen supplementation, n (%) | 87 (51.2%) | -- |
| Respiration insufficiency, n (%) | 18 (16.51%) | |
| Ventilation during hospitalization | 11 (6.5%) | |
| **Comorbidities** | 169 (99.4%) | |
| Cardiovascular diseases | 133 (78.2%) | -- |
| Heart failure, n (%) | 12 (7.1%) | -- |
| Ischaemic heart disease, n (%) | 45 (26.5%) | -- |
| Arrhythmias, n (%) | 33 (19.4%) | -- |
| Peripheral artery disease, (PAD), n (%) | 25 (14.7%) | -- |
| Hypertension, n (%) | 94 (55.3%) | -- |
| Osteoporosis, n (%) | 18 (10.6%) | -- |
| Cancer, n (%) | 17 (10.0%) | |
| Asthma-COPD overlap, n (%) | 24 (14.1%) | -- |
| Pneumonia, n (% | 32 (18.8%) | -- |
| Diabetes, n (%) | 35 (20.6%) | -- |
| Metabolic syndrome, n (%) | 19 (11.2%) | -- |
| **Risk Factors** | | |
| Smoking status | | (9.4) |
| Current smoker, n (%) | 71 (46.1%) | |
| Former smoker, n (%) | 80 (51.9%) | |
| Never smoker, n (%) | 3 (1.9%) | |
| BMI, median [IQR] | 23.4 [20.9, 29.7] | (27.1) |

| | | |
|---|---|---|
| **COPD severity stage** | | (38.8) |
| GOLD I, n (%) | 7 (6.7%) | -- |
| GOLD II, n (%) | 31 (29.8%) | -- |
| GOLD III, n (%) | 37 (35.6%) | -- |
| GOLD IV, n (%) | 29 (27.9%) | -- |
| **Laboratory Values** | | |
| CRP value (mg/L) | 29.00 [7.25,63.75] | (0.6) |
| CRP elevated *, n (%) | 33 (19.5%) | (0.6) |
| Leucocytosis **, n (%) | 76 (45%) | (0.6) |
| Eosinophil count *** ($10^9$/L) | 0.06 [0.01,0.20] | (5.3) |
| **Admission and discharge circumstances** | | |
| Transportation upon admission: ambulance, n (%) | 29 (17.1%) | -- |
| Discharge destination: rehabilitation, n (%) | 38 (22.4%) | |
| **Outcomes** | | |
| Length of stay, in nights, median [IQR] | 8 [6, 11] | -- |
| Rehospitalization within 6 months, n (%) | 76 (44.7%) | -- |
| Death (in hospital death) | 6 (3.5%) | -- |
| Death (one year mortality) | 26 (15.3%) | -- |

* CRP ≥5 mg/L
** Leucocytes elevated >10.5 109/L
*** Eosinophil count normal range <500 109/L)

The median age at admission was 75 years (range 68 - 79) and less than half of the patients were female (46.5%). Vital signs measured at admission revealed that more than half of the patients (51.2%) either received oxygen supplementation or had an indication for it, but only 6.5% required ventilation during hospitalization. The majority of patients (78.2%) had cardiovascular comorbidities, with 55.3% having hypertension, 26.5% having ischaemic heart disease and 19.4% arrythmias. Other comorbidities occurring most frequently were diabetes (20.6%), pneumonia (18.8%) and asthma (14.1%). Regarding risk factors, almost half of the patients were current smokers (46.1%), and the other half (51.9%) were former smokers, whereas less than 2% were lifelong non-smokers. The median body mass index (BMI) was 23.4 with an IQR of 20.9-29.7. In terms of COPD severity based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, the majority of the patients belonged to the GOLD III (35.6%) or GOLD IV class (27.9%). The laboratory values showed that almost 20% of the patients had elevated C-reactive protein (CRP) levels, and 45% had leukocytosis. The median eosinophiles count was 0.06 x 10^9/l with an IQR of 0.01-0.20 x 10^9/l. Regarding discharge destination circa 22% of the patients were discharged for rehabilitation. Out of 170 hospitalized patients with AECOPD, 6 patients died during the hospital stay and were excluded from regression analyses of LOHS and re-hospitalization. Patients with COPD who did not die within the hospital had a median LOHS of 8 nights, with an IQR of 6-11 nights. In total, 26 patients died within one year (15.3% of the total patients) and rehospitalization at the same hospital within 6 months after discharge occurred in 44.7% of the cases.

3.2 Prediction of LOHS, mortality and rehospitalization

Multivariable zero truncated negative binomial regression was conducted to identify predictors of length of hospital stay. The variables entered into the model included age, sex, smoking status, disease severity classification (GOLD stage), comorbidities (cardio-vascular diseases, osteoporosis, active cancer, asthma overlapping, pneumonia, diabetes and metabolic disease), vital signs (indication for oxygen supplementation, respiratory insufficiency), laboratory values (CRP, leukocytosis, eosinophiles) and admission urgency (ambulance transportation). Table 2 provides coefficient estimates for predictors of LOHS in patients who did not die during hospitalization. Regression coefficients are shown as incident risk ratio (IRR). The model showed that indication for oxygen supplementation was the only significant predictor of length of hospital stay (IRR=1.281, CI=1.097-1.496, p-value=0.002). Age, sex, other comorbidities and laboratory values did not significantly predict length of hospital stay in our cohort. The LOHS prediction at the intercept (8.125 days) is the LOHS when all covariates are at 0 (for categorical covariates) or at their mean (for continuous covariates). The predicted LOHS of the model for each variable is presented for one unit increase. Patients who had indication for oxygen supplementation at admission compared to those not requiring oxygen are predicted to remain hospitalized two nights longer (assuming all other variables are held constant), the predicted LOHS rises to approximately 10 days.

Table 2. Results of multivariable zero-truncated negative binomial regression model for length of hospital stay (LOHS) estimation in AECOPD survivors (n =164).

**Table 2.** Results of multivariable zero-truncated negative binomial regression model for length of hospital stay (LOHS) estimation in COPD patients who survived the first hospital admission

| | **LOHS prediction** | **IRR** | **(95%CI)** | | **p-value** |
|---|---|---|---|---|---|
| (Intercept) | 8.125 | 5.647 | 2.83 | 11.267 | 0.000 |
| Sex | 7.550 | 0.928 | 0.789 | 1.092 | 0.368 |
| Age | 8.167 | 1.005 | 0.996 | 1.014 | 0.242 |
| Severe COPD (GOLD III or IV) | 7.718 | 0.949 | 0.805 | 1.119 | 0.534 |
| Heart failure | 7.593 | 0.934 | 0.699 | 1.248 | 0.642 |
| Ischaemic heart disease | 7.090 | 0.871 | 0.731 | 1.037 | 0.119 |
| Arrhythmias | 7.600 | 0.934 | 0.761 | 1.147 | 0.516 |
| Peripheral artery disease (PAD) | 9.106 | 1.122 | 0.91 | 1.384 | 0.281 |
| Diabetes | 7.490 | 0.921 | 0.754 | 1.124 | 0.417 |
| Asthma-COPD overlap | 8.424 | 1.037 | 0.83 | 1.296 | 0.747 |
| Active cancer | 6.462 | 0.792 | 0.608 | 1.031 | 0.083 |
| Ambulance transportation | 8.830 | 1.088 | 0.925 | 1.28 | 0.310 |
| **Indication for oxygen supplementation** | **10.386** | **1.281** | **1.097** | **1.496** | **0.002** |
| CRP | 8.128 | 1.000 | 0.999 | 1.001 | 0.494 |
| Leucocytosis | 7.240 | 0.889 | 0.761 | 1.04 | 0.142 |
| Eosinophils | 5.485 | 0.667 | 0.402 | 1.107 | 0.118 |

Our secondary objectives encompassed the examination of factors linked to mortality and rehospitalization rates. The outcomes of the multivariable logistic regression models for mortality are presented in Table 3. Age, severity of COPD, comorbidities and rehabilitation exhibited significant associations with mortality in patients with AECOPD. Specifically, age (OR=1.105 CI = 1.03-1.194, p-value 0.007), GOLD III or IV (OR = 4.567, CI = 1.357-19.415, p-value 0.023) and active cancer (OR = 7.954, CI = 2.073-32.749, p-value 0.003) were positively associated with an increased risk of death within 12 months of admission. On the other hand, rehabilitation after discharge was negatively associated with mortality (OR = 0.071, CI = 0.002-0.609, p-value 0.049) meaning that people who underwent rehabilitation had higher chances to survive a year after the studied admission. No other variable demonstrated a statistically significant association with 1-year mortality.

**Table 3**. Results of multivariable logistic regression model for one year mortality in patients with COPD

| | **OR** | **(95%CI)** | | **p-value** |
|---|---|---|---|---|
| Sex | 0.481 | 0.141 | 1.547 | 0.227 |
| **Age** | **1.105** | **1.03** | **1.194** | **0.007** |
| **Severe COPD (GOLD III or IV)** | **4.567** | **1.357** | **19.415** | **0.023** |
| Heart failure | 0.809 | 0.089 | 4.586 | 0.826 |
| Ischaemic heart disease | 0.624 | 0.161 | 2.108 | 0.465 |
| Arrhythmias | **7.686** | **2.399** | **27.695** | **0.001** |
| Peripheral artery disease (PAD) | 0.759 | 0.152 | 3.08 | 0.714 |
| Diabetes | 1.929 | 0.541 | 6.662 | 0.299 |
| Asthma-COPD overlap | 0.644 | 0.077 | 3.42 | 0.637 |
| **Active cancer** | **7.954** | **2.073** | **32.749** | **0.003** |
| **Rehabilitation** | **0.071** | **0.002** | **0.609** | **0.049** |
| Length of hospital stay | 0.932 | 0.811 | 1.061 | 0.299 |

Table 4 presents the findings of our secondary multivariable analysis regarding the rate of rehospitalization within 6 months. The logistic regression analysis revealed that none of the variables included in the model showed statistically significant associations with rehospitalization.

**Table 4**. Results of multivariable logistic regression model for rehospitalization in patients with COPD

| | **OR** | **(95%CI)** | | **p-value** |
|---|---|---|---|---|
| Sex | 1.612 | 0.798 | 3.284 | 0.184 |
| Age | 1.027 | 0.989 | 1.068 | 0.169 |
| Severe COPD (GOLD III or IV) | 0.552 | 0.27 | 1.115 | 0.1 |
| Heart failure | 1.446 | 0.416 | 5.331 | 0.562 |
| Ischaemic heart disease | 1.248 | 0.59 | 2.631 | 0.56 |
| Arrhythmias | 0.777 | 0.325 | 1.814 | 0.562 |
| Peripheral artery disease (PAD) | 1.735 | 0.685 | 4.514 | 0.248 |
| Diabetes | 1.353 | 0.586 | 3.157 | 0.479 |
| Asthma-COPD overlap | 1.415 | 0.529 | 3.77 | 0.485 |
| Active cancer | 2.468 | 0.845 | 7.887 | 0.107 |
| Rehabilitation | 1.22 | 0.506 | 2.984 | 0.658 |
| Length of hospital stay | 0.966 | 0.888 | 1.047 | 0.407 |

## 4. Discussion

Our retrospective cohort study is a unique recent investigation conducted in Switzerland, focusing on real-world data, with the aim of identifying possible predictors for LOHS, mortality and rehospitalization in patients with AECOPD. The main findings are that indication of oxygen supplementation at admission was a significant predictor of LOHS and older age, COPD GOLD III and IV and active cancer were significantly associated with higher mortality and rehabilitation after discharge was associated with lower mortality. The logistic regression analysis revealed that none of the variables included in the model showed statistically significant associations with rehospitalization.

The demographic characteristics and outcome variables of our study sample were similar in comparison to other studies. [19–21] Our analysis included 170 patients with a median age of 75 years and a predominance of males in the study population. COPD used to be a condition that mainly affect men. However, in recent years, there has been a significant worldwide increase in the prevalence of COPD among women. As a consequence, global mortality and hospitalization rates related to COPD have increased. [22–24] Data published from the Swiss COPD cohort (timeframe 2005-2014) showed that from a total cohort of 1312 individuals 39.6% were females whereas five years later, in our study, the proportion rose to 46.5%. [2] Given the well-established association between smoking and the development of COPD [25] it is expected that our study population predominantly comprised current or former smokers, accounting for 98% of the sample. Similarly, in terms of comorbidities, our study sample is representative of the overall COPD population, because 84% of the patients had at least one chronic condition which is consistent with previous findings where the proportion was around 80%. [26] Overall the LOHS in patients with COPD has declined significantly in Switzerland over the past 15 years [27]. The average LOHS of our study population (8 days) is in line with the national trend. Moreover, the European COPD Audit in 13 countries which included data from 16 018 hospitalized patients revealed that people with COPD had an average LOHS of 7 days. [13]

Predictors of LOHS, mortality and rehospitalization

As previously mentioned, it was observed in our research that the indication for oxy-gen supplementation at admission was the only significant predictor of the LOHS. The predicted value of hospital stay increased by 2 days (from 8.1 days to 10.3 days) when patients needed oxygen supplementation or their oxygen saturation on admission was < 90%. The need for supplemental oxygen at admission reflects the oxygenation status and the severity of the airflow obstruction and may be an indicator of increased complications. Even though oxygen supplementation has to be applied carefully in COPD with a target oxygen saturation of 88-92% due to the elevated risk of hypercapnia, GOLD and other respiratory societies consider it a key component in the management of severe COPD exacerbation due to its positive effects on patient outcomes. [28–30] The observed significance of indication for oxygen supplementation as a predictor of length of hospital stay is in line with previous research studies including observational and RCTs. [13,31–33]

Our secondary aim was to evaluate the factors associated with mortality in AECOPD. The overall in-hospital morality (3.5%) was lower than that reported in the European audit of COPD in 2013 (4.9%). [34] The study conducted in Switzerland and published by Kutz, et al. in 2019, however, identified a trend where the overall risk-adjusted all-cause in-hospital mortality declined from 4.9% in 2009 to 4.6% in 2015. [27] The analysis of mortality within one year showed that older age, severe airflow limitation, active cancer and arrhythmias were positively associated with mortality and interestingly rehabilitation was negatively associated. Age is a known significant factor associated with mortality across various populations and disease conditions. Therefore, it is not surprising that our study findings also revealed a positive association between age and mortality in individuals with COPD. Numerous studies conducted in different settings have demonstrated that advancing age is associated with increased mortality rates specifically within the COPD population. [34–38] The underlying mechanisms contributing to this association are multifactorial and complex. Aging is accompanied by physiological changes, including a decline in organ function, compromised immune response, and an increased susceptibility to comorbidities. These age-related factors can lead to increased complications and contribute to adverse outcomes, ultimately leading to higher mortality rates. Healthcare providers should therefore identify older individuals with COPD who may be at higher risk of mortality and tailor their treatment plans accordingly. Close monitoring, early intervention during exacerbations, and comprehensive management of comorbidities are crucial for optimizing outcomes in this vulnerable population. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity stage classifies COPD into four stages based on airflow limitation (measured by forced expiratory volume in one second FEV1). [28] In accordance with other studies, (34,39–42) we also observed that mortality increased with the severity of airflow limitation, defined by GOLD stages. Particularly, COPD patients classified in the severity GOLD stage III or IV had increased risk of mortality compared to the mild or moderate stage. The alteration in GOLD stages holds promise as a monitoring tool and outcome measure for clinical research. Although the prognostic value of GOLD status is widely known and verified, it is important to note that in our study this value was reported in only 61.2% of cases. Since 2017, GOLD has proposed a symptom- and exacerbation-based categorization system consisting of groups A to D. [43] However, despite our dataset being sourced from

2019, we found that only 37.6% of the patients in our study cohort had documented information regarding their classification into GOLD groups A-D. As a result, we were unable to incorporate this classification system into our analysis.

Another point worth discussing is the role of comorbidities on mortality. It is already known from the literature that comorbidities are common among people with COPD and they significantly impact patients' survival. [44–46] A strong finding of our research is that arrhythmias emerged as the only significant cardiovascular comorbidity associated with mortality and the most common reason for arrhythmias in our sample was atrial fibrillation (AF). AF is a common type of arrhythmia characterized by irregular heart rhythms originating from the atria. It can lead to poor blood flow, thrombosis, and other cardiovascular complications. [47,48] The association between AF and mortality in patients with COPD exacerbation is consistent with previous research findings. [49–51] These studies have demonstrated that the presence of AF is an independent predictor of adverse outcomes, including increased mortality among patients with COPD. The identification of arrhythmias, particularly AF, as a significant comorbidity associated with mortality highlights the importance of considering cardiac complications in COPD patients. The other significant comorbidity was active cancer. The role of cancer in all-cause mortality aligns with existing evidence and supports the notion that active cancer is a well-established factor associated with increased mortality. [52–54] Moreover it is worth mentioning that some comorbidities are also associated with tobacco usage which is the main cause of COPD, including coronary heart disease, congestive heart failure, and especially lung cancer. [55–58]. However, except for lung cancer these comorbidities did not show a significant association with mortality in our study. Finally in order to control for the potential confounding effect of pneumonia we conducted a sensitivity analysis. The results of the models aligns with the primary models, providing additional evidence of the robustness and consistency of our findings (the sensitivity analysis results are displayed in the appendix tables).

Interestingly, our results suggest that rehabilitation after hospitalization for AECOPD is associated with improved outcomes and a reduced mortality. This highlights the importance of incorporating rehabilitation interventions into the comprehensive management of patients with AECOPD. Particularly pulmonary rehabilitation programs implemented after an acute exacerbation of COPD have been confirmed to be associated with a significant reduction in mortality. [34,59–61] These findings support current guideline recommendations for pulmonary rehabilitation after hospitalization for AECOPD. A notable modification in the GOLD 2023 report is the increased focus on reducing mortality as a primary objective of treatment, which is reflected in the inclusion of a novel segment titled "Therapeutic interventions to decrease COPD mortality". [62] This report highlights the role of non-pharmacological interventions such as pulmonary rehabilitation in reducing mortality.

Concerning our secondary analysis assessing the association of parameters with re-hospitalization within six months, our findings highlight the unpredictability of rehospitalization based on demographic factors, comorbidities and laboratory values at admission in patients with AECOPD and emphasize the need for comprehensive variable inclusion in future studies. Variables that indicate the course of the disease, such as exacerbation history and symptom severity (e.g., GOLD ABCD classification), should be considered in the development of future prediction models. Incorporating these factors into the predictive model may enhance its accuracy and provide clinicians with valuable insights for identifying patients at higher risk of rehospitalization.

Strengths, limitations, and further research

The novelty of our study is that our analysis expanded its focus to encompass a range of factors including demographic factors, health-related factors, and laboratory values available at the time of admission. A further strength was being able to investigate long-term outcomes such as mortality within one year as this data was available for all patients. Moreover, all statistical analyses that were primarily performed on imputed data have also been applied to the non-imputed dataset, the statistical significance of the variables with missing data did not differ in the two datasets. The sensitivity analysis demonstrated that the internal validity of our research was not impacted by missing data. There are some limitations to this study. Being a retrospective study, the data quality depends on precise documentation in the patient files. The data collection process might have resulted in incomplete documentation, leading to missing information, particularly details about smoking including the number of cigarettes smoked daily and cumulative exposure measured in pack-years, which are critical factors in the progression and prognosis of COPD. Moreover, we assumed that if the GOLD status was not reported, the clinician did not assess it, so we could have underestimated the percentage of patients with a GOLD status classification at hospital admission. Additionally, information about rehospitalization within 6 months was only possible within KSBL: due to privacy policy, it was not possible to access information about rehospitalizations in other hospitals. However, in Switzerland readmissions usually occur within the same hospital; a Swiss study has shown that only 17% of unplanned readmissions occurred at a different hospital (41).

General practitioners (GPs) have a unique perspective on COPD management as they provide long-term care and monitoring to patients outside of the hospital setting. They possess valuable insights into the day-to-day fluctuations in symptoms, adherence to treatment regimens, and the effectiveness of interventions implemented in primary care. The combination of GP and hospital data can potentially enhance the accuracy and reliability of predictive models for COPD rehospitalization. By incorporating variables such as exacerbation frequency, medication adherence, smoking status, and GP intervention strategies, researchers can develop robust risk prediction models that encompass both pre-hospitalization and post-discharge periods. Future studies incorporating data obtained from GPs regarding the progression of COPD with hospital records can potentially enhance the accuracy and reliability of predictive models for COPD hospitalization and rehospitalization.

Despite these limitations, our study provides a foundation for future research and contributes with valuable insights into other aspects of COPD, particularly focusing of possible predictors of LOHS, mortality and rehospitalization, available at admission time. The identification of predictors available at admission time might help to promptly identify patients at higher risk of adverse outcomes and consequently healthcare providers can prioritize their care, allocate appropriate resources, and develop personalized management strategies tailored to their specific needs. This proactive approach ensures that patients receive timely and targeted interventions, potentially leading to improved outcomes and a reduced burden on healthcare systems. Furthermore, the ability to identify predictors at admission time facilitates the development of predictive models or risk stratification tools. These tools can assist healthcare professionals in making informed decisions about the level of care required, resource allocation, and appropriate follow-up strategies. By incorporating these predictors into clinical practice, healthcare systems can optimize resource utilization, enhance patient triage, and improve overall healthcare delivery.

## 5. Conclusion

This study identified several predictors for LOHS and mortality, which may further advance our understanding of AECOPD and thereby improve patient management, discharge planning, and hospital costs. In fact, indication for oxygen supplementation at admission was a significant predictor of LOHS, whereas older age, severe airflow limitation and comorbidities were significantly associated with higher mortality, while rehabilitation was associated with lower mortality. The logistic regression analysis revealed that none of the variables included in the model showed statistically significant associations with rehospitalization, emphasizing the need for future, larger studies with a more com-prehensive variable inclusion. Variables that indicate the course of the disease, such as exacerbation history and symptom severity, should be considered in the development of future prediction models. Interestingly, rehabilitation after hospitalization was associated with lower mortality. This potentially protective effect of rehabilitation after hospitalization clearly warrants further confirmation and validation because, due to the non-randomized design of our study, causal inference cannot be drawn. However, rehabilitation has high potential to further improve the comprehensive management of patients with AECOPD.

**Author Contributions:** G.L.-C., M.B. and J.D.L., conceived and designed the research; G.L.-C. and N.O. performed data collection M.B. performed the statistical analysis G.L.-C., M.B. and J.D.L., performed data interpretation; G.L.-C drafted the manuscript and all authors participated in its critical revision. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association. This study protocol was reviewed and approved by the ethics committee of northwest and central Switzerland (Project-ID 2022-00217).

Informed Consent Statement: We included patients whose written informed consent was obtained and patients whose consent exception was permitted by the ethics committee (Art.34 HFG). Patients who denied the hospital's general consent were excluded.

**Data Availability Statement:** All data generated were analyzed during this study and the results included in this article. The data presented in this study are available on reasonable request from the corresponding author. The data are not publicly available due to restrictions in data privacy.

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## 6. Appendix

**Figure A1**. Graph of one year mortality by age groups

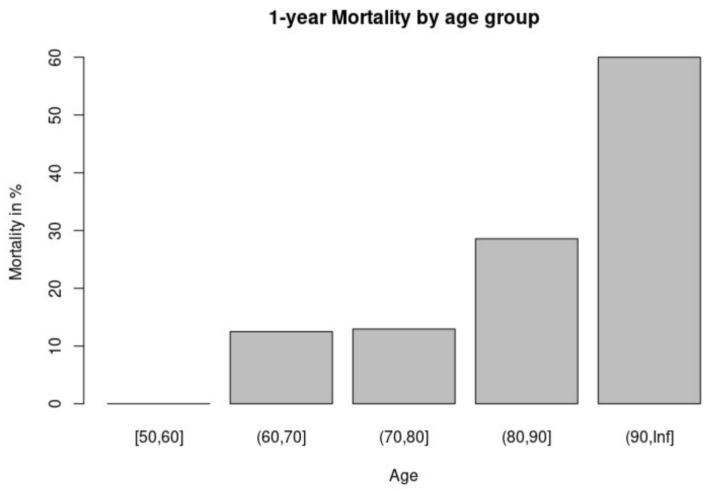


**Table A1.** Sensitivity analysis Results of multivariable zero-truncated negative binomial regression model for length of hospital stay (LOHS) estimation in AECOPD survivors (n =164) controlling for pneumonia.

| | LOHS prediction | IRR | (95%CI) | | p-value |
|---|---|---|---|---|---|
| (Intercept) | 8.333 | 5.33 | 2.683 | 10.59 | 0.000 |
| Sex | 7.808 | 0.936 | 0.797 | 1.099 | 0.421 |
| Age | 8.384 | 1.006 | 0.997 | 1.015 | 0.169 |
| Severe COPD (GOLD III or IV) | 7.931 | 0.951 | 0.809 | 1.119 | 0.546 |
| Heart failure | 7.758 | 0.93 | 0.698 | 1.239 | 0.62 |
| Ischaemic heart disease | 7.369 | 0.883 | 0.742 | 1.049 | 0.157 |
| Arrhythmias | 7.726 | 0.926 | 0.756 | 1.134 | 0.459 |
| Peripheral artery disease (PAD) | 9.413 | 1.131 | 0.918 | 1.392 | 0.247 |
| Diabetes | 7.691 | 0.922 | 0.757 | 1.123 | 0.42 |
| Asthma-COPD overlap | 8.638 | 1.037 | 0.832 | 1.292 | 0.747 |
| Active cancer | 6.613 | 0.79 | 0.608 | 1.027 | 0.078 |
| Ambulance transportation | 8.933 | 1.073 | 0.913 | 1.261 | 0.395 |
| **Indication for oxygen supplementation** | **10.962** | **1.318** | **1.126** | **1.542** | **0.001** |
| CRP | 8.339 | 1.001 | 1 | 1.002 | 0.231 |
| Leucocytosis | 7.47 | 0.895 | 0.767 | 1.045 | 0.16 |
| Eosinophils | 5.715 | 0.679 | 0.412 | 1.121 | 0.13 |
| Pneumonia | 6.898 | 0.825 | 0.666 | 1.022 | 0.079 |

**Table A2. Sensitivity analysis .** Results of multivariable logistic regression model for one year mortality in patients with COPD controlling for pneumonia.

| | **OR** | **(95%CI)** | | **p-value** |
|---|---|---|---|---|
| Sex | 0.465 | 0.132 | 1.532 | 0.216 |
| **Age** | **1.104** | **1.029** | **1.193** | **0.008** |
| **Severe COPD (GOLD III or IV)** | **4.527** | **1.348** | **19.225** | **0.024** |
| Heart failure | 0.825 | 0.091 | 4.67 | 0.842 |
| Ischaemic heart disease | 0.62 | 0.158 | 2.104 | 0.461 |
| Arrhythmias | 7.88 | 2.426 | 28.768 | 0.001 |
| Peripheral artery disease (PAD) | 0.76 | 0.151 | 3.108 | 0.717 |
| Diabetes | 1.981 | 0.548 | 6.947 | 0.285 |
| Asthma-COPD overlap | 0.661 | 0.079 | 3.522 | 0.658 |
| **Active cancer** | **8.084** | **2.096** | **33.66** | **0.003** |
| **Rehabilitation** | **0.07** | **0.002** | **0.604** | **0.048** |
| Length of hospital stay | 0.934 | 0.812 | 1.064 | 0.313 |
| Pneumonia | 1.205 | 0.296 | 4.372 | 0.782 |

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# CHAPTER V

## Conclusions

## 1. General conclusions

In order to support hospital management in the process of improving the quality of care, it is necessary to build new strategies based on evidence-based research.

Defining the factors that are associated with key quality indicators, especially LOHS, rehospitalization and mortality is fundamental to advancing our understanding of healthcare delivery and thereby improving patient management, discharge planning, and hospital performance.

In our three retrospective cohort studies on which this PhD thesis is based, we were able to identify several predictors for LOHS, rehospitalization and mortality in three main acute conditions that lead to hospitalization, namely PE, CAP and AECOPD.

The results of the PE cohort study showed that PESI score (which includes sex, age, medical history and vital signs) is a major predictor of LOHS, mortality and rehospitalization in PE patients. In addition to PESI, diabetes and increased serum troponin at admission are significantly associated with LOHS whereas increased NT-pro- BNP is a predictive risk factor for mortality and LOHS for rehospitalization within 6 months.

The results of the CAP cohort study showed that sex, age, qSOFA score and atypical pneumonia were predictive of LOHS. Diabetes, a high qSOFA score and rehabilitation after discharge were associated with a higher chance to be rehospitalized within 6 months, whereas mortality within 30 days and within one year were both linked to higher age and the presence of a cancer diagnosis.

The main findings of the AECOPD cohort study are that the indication for oxygen supplementation at admission was a significant predictor of LOHS; older age COPD GOLD III or IV and active cancer were significantly associated with higher mortality, while rehabilitation after discharge was associated with lower mortality.

Overall, the following conclusions can be drawn from these studies:

Disease-specific factors available at admission time can accurately predict LOHS, in particular when the predictive model takes variables with a broader focus beyond merely demographic characteristics into account.

Our findings from the PE cohort study, in fact demonstrate that the accuracy of the LOHS predictive model is higher when also factors of the healthcare system, processes and outcome indicators are included (namely PESI score, BMI, medical history of dyslipidemia, diabetes or previous PE, NT-proBNP and troponin-T hs, housing situation before admission and admission via GP).

Risk scores commonly used to predict 30-days mortality or sepsis (like PESI score for PE and qSOFA for CAP) can be also considered significant predictors for LOHS and rehospitalization within 6 months. Moreover, our study confirmed the essential role of PESI score calculation in the management of PE patients, which clinicians and GPs should be aware of and perform the calculation as soon as PE is diagnosed.

Among demographic characteristics the only factor that was predictive for LOHS and mortality in all three conditions (PE, CAP and AECOPD) was age. Our findings highlight the importance of the impact of aging on health outcomes in terms of both patient related and healthcare system outcomes.

It is worth to mention that among the comorbidities cancer and diabetes mellitus were the only two significant predictive conditions., Specifically cancer was predictive for higher risk of mortality for both PE and CAP patients, whereas diabetes mellitus was associated with longer LOHS and with rehospitalization (within the PE and the AECOPD cohort study, respectively).

Finally, our findings highlighted the unpredictability of rehospitalization based on demographic factors, comorbidities and laboratory values at admission in patients with AECOPD and emphasized the need for comprehensive variable inclusion in future studies. Variables that indicate the course of the disease, such as exacerbation history and symptom severity (e.g., GOLD ABCD classification [1]), should be considered in the development of future prediction models. Incorporating these factors into the predictive model may enhance its accuracy and provide clinicians with valuable insights for identifying patients at higher risk of rehospitalization.

## 2. Strengths and limitations

The major strengths of the three cohort studies that form the foundation of this PhD research can be summarized as follows: comprehensive variable focus, robust methods and long-term outcomes.

### I. *Comprehensive Variable Focus*

One of the primary strengths of our cohort studies is the comprehensive focus on variables as predictive factors. We conducted a literature review and consulted clinical experts in the field. We have meticulously

selected a diverse set of variables related to the four main areas of predictors including healthcare system factors, patient characteristics, processes, and outcome indicators.
The inclusion of a broad spectrum of predictive factors enables a better understanding of the complex interactions underlying LOHS, rehospitalization, and mortality outcomes ultimately leading to improved clinical decision-making and resource allocation.

II. *Robust methods*

To minimize the risk of bias, optimism, and overfitting, no data-driven selection of variables was done. We selected potential predictors based on the literature and clinical knowledge. The researchers have taken potential confounding factors into account, ensuring that the identified associations are robust and meaningful.
Our cohort studies employ advanced statistical methods to analyze the relationships between predictive factors and outcomes. Among these methods, the multivariable zero-truncated negative binomial regression analysis stands out as particularly effective in modeling count data with a skewed distribution, which is typical for LOHS. This approach allows us to effectively handle the overdispersion of the outcome variables and incorporate multiple predictors simultaneously, providing a more accurate representation of the underlying relationships.
In addition to the primary analysis, we have also conducted sensitivity analyses to assess the robustness of our findings. These sensitivity analyses involve testing the impact of different assumptions or exclusions on the study results. By conducting such analyses, we ensure that our conclusions are not heavily dependent on specific model specifications and that the identified associations hold under various scenarios.
Another key strength of our cohort studies is the use of comparable samples in relation to other studies in the field. The patient characteristics of our three cohorts are similar to those of other Swiss, European and American studies and therefore representative of the target population. By doing so, we enhance the external validity of our findings, making them more generalizable to broader populations.

III. *Analysis of Long-Term Outcomes*

The consideration of long-term outcomes, including rehospitalization within 6 months and mortality within 1 year, is a crucial strength of our cohort studies. By assessing the impact of predictive factors on both short-term and long-term outcomes, we gain a more comprehensive understanding of the patients' health and outcomes over time.

This long-term perspective allows us to identify predictors that may have a delayed or cumulative effect on patient outcomes, highlighting potential intervention points for healthcare providers and contributing to a more holistic understanding of disease progression and recovery patterns.

In conclusion, the three cohort studies forming the basis of this PhD research possess significant strengths that contribute to the scientific rigor and relevance of the findings. They underscore the potential impact on patient care and health policy decision-making.

Despite the above-mentioned strengths, the three studies have some common limitations. Firstly, they all share a retrospective observational study design, which means that the data quality mainly relies on accurate documentation in patient files, leading to potential incomplete information. The use of imputation for missing data allowed us to include most available data in the multivariable models, but it does not come without risks. We tried to minimize these by carefully choosing the imputation method, by not using data-driven variable selection and performing the sensitivity analyses mentioned above. Moreover, although we controlled for confounders and therefore minimized the risk of bias, the study design only allows us to detect associations and we cannot draw conclusions based on a causal relationship. Secondly, privacy policies restricted access to information about rehospitalizations in other hospitals, limiting the ability to capture all rehospitalization events. However, studies show that in Switzerland, most unplanned readmissions occur within the same hospital, reducing this limitation's impact. Furthermore, there is a need for future research to validate and refine the predictive models used in these studies, preferably in multicenter studies with larger sample sizes to enhance accuracy and generalizability. Lastly, certain specific factors were not included in the analysis due to missing documentation or limitations in data collection, such as smoking status for the CAP cohort study and GP-related variables for the COPD cohort study. Addressing these gaps could further enhance the predictive capabilities of the models and provide more comprehensive insights into the studied conditions.

## 3. Future studies

The PhD project contributed to further advancing the understanding of factors that are associated with LOHS rehospitalization and mortality in patients hospitalized for PE, CAP and AECOP. In addition, from our findings, we identified challenges that will be further investigated within three main research projects, the QUA-DIT project, the PRO-LAB project and the SHARE project.

### 3.1. The QUA-DIT project

*"Evaluation of hospital care quality through audits"*

In order to further assess the quality of health care delivery in public hospitals, with the QUA-DIT project, we seek to identify disease-specific areas of in-hospital management where diagnostic and/or therapeutic guideline-adherence is suboptimal and we plan to investigate the effect of guideline-adherence on patient outcome-related quality indicators (LOHS, rehospitalization and mortality). The QUA-DIT project consists of seven clinically driven audits in typical acute diagnoses in the department of internal medicine at the Cantonal Hospital Baselland. Recent clinical routine data concerning diagnostic workup, treatment, and other measures of care will be collected and descriptively compared to the established national and international disease-specific guidelines. Ultimately, the association of guideline-adherence with the quality indicators (LOHS, rehospitalization and mortality) will be assessed by multivariable regression models. We expect to include data from 2410 patients in our analyses.

Establishing a series of clinical audits that employ the same methodology, aiming to improve quality in different fields of internal medicine is an innovative approach. Based on the audit findings, we plan to implement several measures to achieve improvement in the evidence-based management of our patients, with a view to re-auditing thereafter. Transparent publication of the results is a way of creating awareness in the internal medicine community and may serve as a motivation for other hospitals to follow this example. The QUA-DIT project is in line with the smarter medicine initiative and is a significant, financeable and implementable step in improving the overall healthcare system, and ultimately improving the health of the population.

### 3.2. The PRO-LAB project

*“**PRO**spective observational cohort study assessing the predictability of **LAB**oratory values in patients outcomes”*

As previously discussed, our study revealed that higher serum troponin was significantly associated with LOHS, whereas increased NT-proBNP levels were associated with mortality [2], but this difference in research has not been deeply investigated yet [3].

Moreover, although in other conditions like acute coronary syndrome, the level of NT-proBNP provided better predictive power than troponin, this difference in PE patients has still to be established [4]. Since our retrospective data had several missing laboratory values, we could not draw conclusions on causal inference. Moreover, in case doctors prescribe laboratory analysis only when they believe there is a serious cardiac condition, the predictive value of biomarkers can be biased, so it will be important to prospectively investigate if these results are confirmed when NT-pro-BNP and troponin are measured in all patients hospitalized for PE, independent of the patient’s symptoms, history and preferences of treating physicians.

Ultimately, the precise role of biomarkers in early risk stratification is fundamental since PE may present with a wide spectrum, but unspecific symptoms. Biomarkers might be crucial in order to detect a serious condition and consequently allow treatment adjustment with a more targeted therapy.

The primary aim of the study will be to determine the predictive role of serum NT-pro-BNP and troponin at admission in terms of length of hospital stay in patients with PE. Secondary endpoints are mortality (in-hospital, 30 days, 90 days) and rehospitalization within 6 months.

The PRO-LAB study will provide valuable information on the predictive ability of NT-pro-BNP and Troponin in patients with PE. The findings of this study may guide the development of risk stratification algorithms and inform clinical decision-making in this patient population.

### 3.3. The SHARE project

*"**S**electing and sharing **H**ospital d**A**ta for **R**esearch and **E**vidence-based medicine"*

The PhD project highlighted the importance of the use of routine clinical data with big datasets for research, evidence-based medicine and personalized health.

Progress in developing novel diagnostic, therapeutic and prognostic strategies is currently limited by the challenge of accessing large clinical datasets ("big data"), the existence of data in a variety of different formats, and the difficulties concerning linking different data sources for profiling individual patients or patient groups.

One main challenge of data collection is that patient medical data are recorded as a mix of unstructured paper-based documents and digital data that are neither easily accessible nor suitable for solving complex clinical problems or for performing clinical research projects. While the identification of patient cases is possible in most digital clinical information systems via keyword searches for defined terms, the identification and extraction of further relevant case-related information such as patient characteristics, diagnostic procedures and results, clinical course of hospitalization, final diagnosis and therapy remains a great challenge. To collect such data, manual search processes are usually required that are time-consuming and can lead to errors, making a broad case search across multiple hospitals or hospital sites extremely complex, if not impossible. Nevertheless, to answer scientific questions, a targeted collection of comprehensive clinical datasets on as many individual patients as possible is necessary to obtain valid conclusions.

With the **SHARE** project we aim to demonstrate the ability to:

- access unstructured data and combine it with structured data, making data from different systems and formats accessible,
- make data available for big data research for personalized health and evidence-based medicine.

We foresee a pilot study based on the collection of PDF reports from patients who presented at the ED with dyspnea as chief complaint and were hospitalized to internal medicine during the year 2022. A total of approximately 3,000 PDFs will be collected.

The results of the pilot study will provide initial insights into the feasibility and performance of the new system for extracting unstructured medical data from PDF reports. The results will help determine the accuracy, specificity, and sensitivity of the system in identifying dyspnea cases and extracting relevant information from medical reports.

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