Serious Conditions in Patients Presenting with Non-Specific Chief Complaints to the Emergency Medical Service (EMS)

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To Annika, Malte, Henning and Hedda

"Research is the process of going up alleys
to see if they are blind."

Marston Bates

ABSTRACT

BACKGROUND

Ambulance clinicians encounter patients presenting with non-specific chief complaints on a daily basis. Such complaints can also be described as "decreased general health condition" "general malaise" and "sense of sickness". These symptoms are often accompanied by vital signs within the normal reference range. It is known that one in three patients in the emergency department presenting with non-specific chief complaints have underlying serious conditions. In the context of ambulance care, there is a lack of knowledge in the group of patients and the identification of serious conditions within that group.

AIM

The overall aim was for patients with non-specific complaints in the pre-hospital setting; to describe the population for both those who are transported to hospitals or not i.e., conveyed, or non-conveyed, to investigate whether biomarkers can contribute to the identification of those who develop a serious condition, and to describe the experiences of pre-hospital emergency nurses in caring for the patient.

METHODS

Four sub-studies were performed. **Study I** was a retrospective, population-based study with the aim to describe the population and establish the prevalence of serious conditions as well as mortality rates among patients presenting with non-specific chief complaints and who were transported to the ED. Patients were identified via the electronic ambulance medical records (CAK-net, Region Stockholm) and data was retrieved from the National Patient Register and Causes of death register at Sweden's National Board of Health and Welfare. Descriptive statistics was performed. **Study II** was a retrospective, population-based study with the aim to describe the population, establish the prevalence of serious condition as well as mortality rates and to compare between the groups of patients who were conveyed or non-conveyed. Descriptive statistics and regression analysis was performed. **Study III** was a qualitative interview study of prehospital emergency nurses experiences in caring for patients presenting with non-specific chief complaints. Qualitative content analysis according to Elo and Kyngäs was performed. **Study IV** was a prospective, double-blind, multicenter study with the aim to determine if the biomarkers suPAR and lactate could identify serious conditions, as well as the predictive value on mortality. Ambulance care systems from Stockholm Region and two regions of Helsinki, Finland participated. Two blood tests were drawn after index ambulance

assessment. Descriptive statistics as well as regression and likelihood analyses were performed.

RESULTS

In **Study I**, 3780 patients were included and had a median age of 77 years. Serious condition was prevalent in 35.3%. Admittance to hospital care was 67.7%. Patients with prevalent serious conditions had 20.2% 30-day mortality compared to 4.2% in the group without serious conditions. The majority of the patients had low triage scores according to Rapid Emergency Triage and Treatment System (RETTS) (60.7%) and National Early Warning Score (NEWS) (76.3%) and 23.9% and 28.3% had prevalent serious conditions respectively. 30-day mortality was 13.0% and 14.1% respectively. In **Study II**, a total of 4744 patients were included, with a median age of 76 years. A serious condition was present in 29.5% of the patients. Among those who were non-conveyed, serious conditions was present in 6.6% compared to 35.3% among those conveyed. 30-day mortality was 17.2% for those with prevalent serious conditions and who were non-conveyed, compared to 20.2% in the group who were conveyed. In **Study III** the prehospital emergency nurses expressed that an in-depth systematic assessment may reduce suffering and increase patient safety. The systematic assessment is based on acknowledging the unexplained suffering, a systematic approach and experience, and that organizational processes such as feedback on given care are key for a meaningful caring encounter and optimal assessment. In **Study IV**, a total of 414 patients were included. The median age was 82 years of age. 15.2% of the patients had a serious condition. A positive likelihood ratio (LR+) of 1.17 and a positive predictive value (PPV) of 17.3% as being predictive of a serious condition was observed when suPAR was elevated above 3 ng/ml. A LR+ of 4.67 and a PPV of 16.7% was observed for suPAR levels above 9 ng/ml as being predictive of 30-day mortality. Lactate was not significantly predictive.

CONCLUSIONS

Several conclusions stem from the findings in the four sub-studies. The results indicate that the identification of serious conditions among patients presenting with non-specific chief complaints to the ambulance service is still complicated. Serious conditions are present in both high and low triage levels. These triage systems are based on vital signs and may therefore be insufficient tools with which to identify serious conditions. The patients who are non-conveyed after index assessment do not differ from the patients conveyed in term of symptoms, sex or age. However, they differ in terms of prevalence of serious conditions and mortality, which is in both cases lower. The biomarkers, suPAR and lactate cannot

differentiate between patients with or without serious conditions, but the association with mortality could add value to the clinical assessment. Prehospital emergency nurses experience that this patient group benefits from an in-depth systematic assessment that can reduce suffering and increase patient safety, and that organizational factors such as feedback and differentiated levels of care could have positive effects on care in general and for patients with non-specific chief complaints in particular. The results indicate that the assessments are complex and that the objective parameters used are not sufficient to identify serious conditions. Identification of serious conditions among patients presenting with NSCs to the ambulance service remains a challenge. Increased education and feedback on given care would likely increase the identification. However, an enhanced understanding of the atypical presentations of NSCs and the process of clinical reasoning could strengthen the ACs in performing person-centered care.

LIST OF SCIENTIFIC PAPERS

I. **Ivic R**, Kurland L, Vicente V, Castrén M & Bohm K. Serious conditions among patients with non-specific chief complaints in the pre-hospital setting: a retrospective cohort study. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 2020*;28(1):74. doi: 10.1186/s13049-020-00767-0

II. **Ivic R**, Kurland L, Vicente V, Arvidsson E, Castrén M & Bohm K. Non-specific chief complaints and serious conditions in Emergency Medical Services – a retrospective comparison of non-conveyed and conveyed patients. *Manuscript.*

III. **Ivic R**, Vicente V, Kurland L, Svensson J, Sahdev Klintemård R, Castrén M & Bohm K. Pre-hospital emergency nurse specialist's experiences in caring for patients with non-specific chief complaints in the ambulance - A qualitative interview study. *Submitted 2021.*

IV. **Ivic R**, Nurmi J*, Kurland L, Vicente V, Lindström V, Djärv T, Kaartinen J, Castrén M & Bohm K. Soluble urokinase plasminogen activator receptor and lactate as prognostic biomarkers in patients presenting with non-specific chief complaints in the pre-hospital setting - the PRIUS-study. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 2021;*29(1):116. doi: 10.1186/s13049-021-00908-z

CONTENTS

LIST OF ABBREVIATIONS

AC	Ambulance clinician
AISAB	Ambulanssjukvården I Storstockholm AB (Ambulance care in Greater Stockholm Ltd)
ALS	Advanced Life Support
AMLS	Advanced Medical Life Support
AUROC	Area under receiver operating characteristics
BLS	Basic Life Support
CCI	Charlson Comorbidity Index
CI	Confidence Interval
ED	Emergency Department
eHR	Electronic Health record
EMCC	Emergency Medical Communication Centre
EMS	Emergency Medical Service
EMT	Emergency Medical Technician
ESS	Emergency Symptoms and Signs
GCS	Glasgow Coma Scale
HEMS	Helicopter Emergency Medical Service
ICD-10	International Classification of Diseases, Tenth Revision
IQR	Interquartile range
LOS	Length of stay
LR+/-	Positive / negative likelihood ratio
MICU	Mobile Intensive Care Unit
NACA	National Advisory Committee for Aeronautics
NEWS	National Early Warning Score
NPV	Negative predictive value
NSC	Non-specific chief complaint
OR	Odds ratio
PEN	Prehospital Emergency Nurse
POC/POCT	Point-of-care / point-of-care test
PPV	Positive predictive value

PRIUS	Pre-hospital Recognition and Identification of Unspecific Symptoms
RETTS	Rapid Emergency Triage and Treatment System
RRU	Rapid Response Unit
suPAR	soluble urokinase plasminogen activator receptor

Definition of Ambulance service and emergency medical service (EMS)

In this thesis, Ambulance service is defined as the service and care provided by ambulance clinicians who are employed by the organization responsible for providing pre-hospital emergency medical care. Emergency medical service (EMS) is considered from the broader definition of the system, comprising agencies and organizations, communications, and transportation as well as trauma systems and hospitals. In studies I, II and IV, the use of EMS is considered interchangeable with ambulance service, and in this thesis the use of the narrower ambulance service is considered to better reflect the setting.

Definition of conveyance and non-conveyance

In this thesis, conveyance is defined as the patient being transported to an ED.

Non-conveyance is defined as the decision not to transport the patient to the ED after EMS assessment. In Stockholm Region non-conveyance guidelines may be applied only if the patient is triaged to the lowest category in EMS, or refuses conveyance after assessment.

1 INTRODUCTION

Patients in the field of emergency medicine, and in the ambulance service, present with a symptom rather than a diagnosis. Most of the patients can present a specific symptom or complaint, some may even be recognized by the clinicians without asking questions due to the obvious anatomical appearance. This thesis will focus on the complete opposite. Patients presenting with complaints they cannot describe or explain.

Ambulance clinicians are daily dispatched to patients seeking help for complaints which cannot be pinpointed within the specific spectrum. Patients may present only with a sense of being sick or tired beyond the ordinary with a relatively short onset time. When assessed by the ambulance clinicians using the ordinary toolbox consisting of a few simple vital signs the patients may be triaged to a low urgency score and could expect long waiting times at the emergency department if transported.

Prior to the scientific journey resulting in this thesis, I heard the words "why are ambulances wasting time on patients not requiring acute medical attention?" more than a few times. Naturally, the question could be tackled by confirmation and support for the statement or a deeper thought if there was something more to it, that we did not know of yet. I chose the latter.

Reviewing the literature for answers or hints on how to assess and handle patients with unclear complaints led to the focus-point of this thesis, the non-specific chief complaints and further down the road to the prevalence of serious conditions among patients presenting with non-specific chief complaints. The challenges ambulance clinicians face when encountering this group of patients begins even before they are dispatched, when the emergency medical communication centre receives the call and have the challenging task to categorize and prioritize the individual's care needs. The challenge in identifying the cause of the complaint persists from the pre-hospital setting to the hospital setting.

2 LITERATURE REVIEW

Along with a growing population and a limited number of hospital beds, an increased strain can be noted in the health-care system. In the prehospital setting, the ambulance service plays an important role in assessing, initiating treatment, and transporting patients to the Emergency Department (ED). The patients are assessed based on vital signs and patient history, according to local pre-hospital medical guidelines [1]. All patients assessed by the ambulance clinicians (ACs) in Stockholm Region are granted conveyance to the ED [2]. Emergency medicine comprises the entire chain of emergency care from the call to the emergency medical communications center (EMCC), the priority, assessment and treatment of the ambulance service, to the conveyance to hospital and the ED. In year 2017, the Stockholm Region received one million 112-calls of which 260 705 were medical emergency calls. In total, 210 717 of the emergency medical calls were dispatched. Out of those approximately 12 000 (5%) had non-specific chief complaints [3]. EDs in Stockholm Region received a total of 401 574 visits in year 2017 [4]. Patients present to the emergency care with a symptom, not a diagnosis [5]. It is utterly important to be able to identify those with serious conditions in need of treatment. To guarantee safe and effective medical attention, decision support tools are needed.

2.1 The ambulance service in Stockholm region

The Stockholm Region is responsible for the ambulance service and the service is provided by one organization within the region and three private companies contracted by the region. The ambulance assignments are distributed among 83 ambulances, eight transport ambulances, one bariatric ambulance, one psychiatric response unit, three mobile intensive care units (MICU), two helicopter emergency medical service units (HEMS), three on-scene command units, three rapid response units and three primary care units. The Swedish ambulance service have undergone a process of change during the recent decades from being an emergency medical technician (EMT) based organization to a nurse-based organization due to formal regulations that stipulate that the administration of drugs is reserved for registered clinicians only [6]. Several regions – the Stockholm region included - have further increased the formal requirements, and today ambulances in Stockholm are manned by at least one registered nurse with an additional one-year national specialist education at university level, including a master thesis. The level of higher education is a minimum of 4 years or 240 credits [3]. The other member of staff can be either a registered nurse without a

specialist degree, equivalent to a bachelor's degree in nursing which consists of 180 credits, or an EMT. The EMT has a high school diploma in nursing and care and is eligible to work as an assistant nurse. EMT training consist of 40 weeks of theoretical and 3 weeks practical education. The rapid response units (RRU) are manned by one physician and one registered nurse with a specialist degree. Two of the RRUs are manned by a physician in emergency medicine and a nurse anesthetist, while one RRU is manned by an anesthesiologist and a pre-hospital emergency nurse (PEN). The primary care units are manned by a physician in primary care and an EMT. Pre-hospital care and emergency medicine are complex environments, prone to risks in patient safety. The National Board for Health and Welfare in Sweden implies that patient safety risks can be decreased by increased competence and adequate staffing and organization [7].

2.2   Pre-hospital emergency nurses assessment and reasoning

Many of the registered nurses with a specialist degree in the ambulance service have a professional degree in Specialist Nursing in Prehospital Emergency Care, with a restricted professional title of "pre-hospital emergency nurse (PEN)". PENs work independently and provide care for patients bort in emergencies and in less serious situations. The competencies consist of among others: professional skills, professional judgement, technical skills, pedagogic skills, interpersonal communication, and leadership [8]. The PEN should be able to create a preparedness for unforeseen and varying tasks where the information is often deficient [9]. PENs must be able to quickly assess and prioritize the patient with acute and life-threatening conditions. The competence includes knowledge of sick and / or injured patients of all ages and an effort to try to understand what has happened. They should also be able to show care and respect for integrity and dignity. An ethical approach should characterize the care work and each patient must be met as a unique individual with unique needs and with regard to the patient's own experiences [10].

In order to achieve a care relationship, an interaction is required in the meeting between the patient - the person receiving care, and the caregiver - the one providing care. The care relationship is based on respect, commitment and the caregiver taking part in the patient's experiences and acknowledging their experiences [11, 12].

The assessments performed by ACs and PENs among them, are based on both objective measurements of vital signs and subjective findings from the patients' narrative. The assessments based on objective patient data can be seen as a diagnostic reasoning behavior, a

sort of analytical decision-making process [13]. The assessments based on the patient's narrative, where the patient's perspective and experiences are included can be regarded as a part of a larger whole [9, 14]. The level of knowledge and clinical experience is viewed as important when assessing and reasoning with the aim to identify the individual patient's needs [15]. The assessments differ between clinicians depending on the influence of experience and subjectivity [16]. Clinical reasoning is considered as an important part of the clinical assessments, ranging from unreflecting response to sudden changes in the clinical environment and patient's status, to a more slow process consistent of reflection and analysis, allowing the clinician to collect more information before making a decision [17].

Specialist nurse studies at the university have been shown to lack educational parts involving caring for patients with non-urgent needs, including NSCs [18] with the risk of not being adequately prepared for one's clinical work. Such unpreparedness can lead to frustration and compassion fatigue [19]. The latter is a risk for negatively affecting patient safety [20].

2.3 Non-specific chief complaints

The presenting symptoms which this research project is based upon are non-specific chief complaints (NSC). The concept of NSC is new and its definition has not yet been formally established. The most common definition used is the definition by Nemec et al [21] "all complaints that are not part of the set of specific complaints or signs or where an initial working diagnosis cannot be definitively established". Another definition is by Djärv et al [2] "rapid decline of conscious patient's own experience in mental and/or physical condition without signs or symptoms from a specific organ and without ongoing fever". The NSCs can roughly be defined as a lack of specific complaints. Subsumed in the spectra of NSCs, presentations are described as decreased general condition, general malaise, sense of illness, general disability, atypical symptoms, nonspecific functional decline or just being unable to cope with usual daily activities. NSCs as such are often accompanied by normal vital signs. [2, 22-26]. It is also argued that NSCs are one of the top five presenting complaints in the ED and that generalized weakness represent the largest subgroup [5, 21, 27]. Patients in the prehospital setting presenting with NSC are often assessed as "affected general health condition".

The assessment is challenging for the ACs, since it is difficult to distinguish the sick patient from the one who is not in need of further medical attention. Duration of the symptom or perceived illness is crucial for separating newly developed NSCs from long lasting geriatric

symptoms, such as frailty [28]. It requires a higher level of responsiveness and sensitivity to the entire group of patients, since the symptoms are per definition non-specific, and are not accompanied by a specific standard operating procedure [1]. The regional medical guidelines in Stockholm Region cover many specific conditions and symptoms. NSCs are not described more than being encompassed in the general guideline which states that; "in those cases of uncertainty on the best way to assess and treat the patient, and when appropriate guideline is lacking, symptomatic treatment is advised and contact with the pre-hospital physician on-call recommended". Further the guideline states; "in uncertainty on the patient's condition/destination, the patient is transported to the nearest hospital" [1].

Often the clinical picture is complicated by e.g., comorbidity, polypharmacy and altered mental status [21-24]. Previous studies [21, 29] have shown that patients who present to the ED with non-specific chief complaints have a high risk of suffering from an underlying serious condition. Overall, up to 20% of the patients presenting to the ED have no specific chief complaint. These patients are also associated with elevated inflammatory markers [30]. As much as 50% of the elderly with NSCs suffer from an acute medical problem [31]. Many of these patients receive a low triage priority due to lack of deviated vital signs or atypical presentations that do not trigger the triage system [2, 5, 32]. This may be partially explained by the physiological changes in the elderly that lead to those acute diseases often present non-specifically [31]. Weakness, one of the NSCs has been shown as a predictor for hospital admission [33]. Patients presenting to the ED with NSC also demonstrate longer in-hospital length of stays compared to patients with specific complaints that present to the ED [34]. Longer length of stays has previously been found to increase mortality [35]. In addition to longer length of stay, patients presenting with NSCs have a near to 50% risk for incorrect ED diagnosis [36-39]. Patients presenting with "decreased general condition" have the highest in-hospital mortality of all non-trauma/ nonsurgical chief complaints presenting to the ED [5, 40].

2.4   Serious condition

To our knowledge there is no universal definition for serious conditions. Due to the broad spectrum of possible diseases underlying a serious condition presentation, a narrow or disease specific endpoint may not be suitable. In emergency medicine the physician must instead be focused on distinguishing serious from non-serious conditions. Serious conditions can be defined as potentially life-threatening conditions and may include time sensitive conditions,

e.g., myocardial ischemia, stroke, and sepsis [41, 42]. Time sensitive conditions are those conditions where the time to treatment affects patient outcome [21]. In a systematic review [42] these were further defined with the addition of neoplasms, meningitis, dyspnea and chest pain. The European Emergency Data Project identified five conditions as being time sensitive. They were cardiac arrest, respiratory failure, severe trauma, chest pain and stroke. In a pre-hospital setting and hospital emergency care the established concept of Advanced medical life support (AMLS) is widely used. AMLS uses the terms "life-threatening", "non-life-threatening/emergent" and "non-emergent" when categorizing different conditions, such as chest pain. Connecting to chest pain, AMLS also classifies tension pneumothorax, pulmonary embolism, heart failure, aortic aneurysm/dissection, pericardial tamponade and Acute Coronary Syndrome as life-threatening [43]. Another term which needs to be distinguished is critical illness. Critical illness is a condition which is immediately life threatening and if not treated will lead to death within a short time period [44, 45]. Apart from the fact that there is no definition or consensus on serious condition and time critical conditions in particular, the terminology used is also diverse. Wibring et al [41] identified a number of problems associated with the use of the term time-sensitive conditions, where, for example, intoxication could be a minor and low emergent condition, but also life-threatening, depending on the dose and type of substance.

Nemec et al [21] presented a definition of serious condition defined as any potentially life-threatening condition or any condition that requires an early intervention to prevent health status deterioration leading to possible morbidity, disability, or death. Death within 30 days from NSC presentation was defined as due to serious condition. In the current thesis we have chosen to define serious condition in accordance with Nemec et al [21] and taken it another step by operationalizing this list of conditions as International Classification of Diseases, Tenth Revision (ICD 10) codes so as to make data extraction from national registries possible.

2.5   Triage

2.5.1   History of triage

"Triage," "rationing," and "allocation" are terms commonly used to refer to the distribution of medical resources to patients [46]. The practice of triage was developed by the military and is closely associated with military medicine. From the first formal battlefield triage system in the Napoleonic era, stating that the most wounded should receive first attention,

without regard of rank or distinction, to the mid-19th century, streamlining the focus on those who need immediate treatment and for whom treatment is likely to be successful [46, 47]. The methods for triage and different models evolved through war-time milestones and adapted some of the medical breakthroughs. These technical and medical improvements have led to even more precise triage and decreasing mortality in the group of wounded.

2.5.2 Triage models

Triage as noted above, is in its primary sense the sorting of patients for treatment in situations of at least modest scarcity. Different triage models exist due to the different types of environments they are applied in. Different models are based on the ratio of resources to the number of patients needing evaluation and treatment [48-50]. ED triage systems are designed initially as, "How long can the patient safely wait to see a doctor?" and have been developed in parallel with increased patient ED inflow in turn limiting resources. The systems aim to identify the most urgent, or most serious cases to ensure that they receive priority treatment, followed by the less urgent cases. In an ED, resources are available to treat every patient, although the less urgent must wait longer [48].

2.5.3 Triage in the ambulance service

The first link in the chain of care for a patient with an emergency is the Emergency Medical Communications Centre (EMCC). Most emergency calls in Sweden are received by one of the EMCCs operated by SOS Alarm Sverige AB. A registered nurse, or operator educated in receiving calls but without formal medical education, will speak to the caller/patient. The telecommunicators at the EMCC are assisted in assessing and prioritizing emergency medical calls by Medical Index, a criteria-based dispatch protocol [51]. Medical Index is a three-graded priority protocol, containing 30 chapters based on main complaints. Each chapter is divided into different medical conditions and priority levels. The priority levels assigned by the telecommunicator spans from 1 (the most urgent) to 3 (the least urgent). A fourth level exist and is assigned to callers not requiring medical assistance but only transportation to a hospital or healthcare facility. After assessment and prioritization an ambulance is dispatched for further on-site assessment, treatment initiation and transport to an ED or similar facility [52, 53]. The prehospital assessment in Sweden is based on the Rapid Emergency Triage and Treatment System (RETTS©). RETTS© is a five-level triage scale based on vital signs and 59 chief complaint algorithms known as emergency symptoms and signs (ESS). RETTS© is a development from the original Medical Emergency Triage and Treatment System [54]. The algorithms highest value is considered the most appropriate, i.e., if the patient's vital signs are within normal reference the algorithm will appoint a low triage level, but if simultaneously

the ESS are within a higher triage level, the patient will receive that higher priority and will be treated within the range of the guidelines concerning the condition. The RETTS© triage system is widely spread across Sweden, and both ED's and the ambulance service use it. The nation-wide coverage is 95% [55]. In recent years the call for more precise triage models have emerged in the ED's and the ambulance service. National Early Warning Score (NEWS) is implemented by ED's together with RETTS© for additional risk stratification. The ambulance service has not implemented NEWS into the daily guidelines. NEWS is based on a simple aggregate scoring system in which a score is allocated to physiological measurements via vital signs. The aggregate score is converted in to a three-level scale of risk assessment, low, medium, and high risk [56-58].

2.6   Biomarkers

The severity of the disease state is determined by the degree of systemic inflammation and subsequent hemodynamic changes, the extent of biological stress, organ failure and ultimately death [59]. Therefore, circulating mediators of core pathways may potentially serve as prognostic biomarkers [59]. Point-of-care (POC) blood tests are rapid, bedside laboratory tests, where laboratory setting for analysis is not required [60]. Point-of-care-testing (POCT) makes testing in out-of-hospital settings, i.e., in the ambulance possible, and is used in clinical decision-making guidelines. In Stockholm Region the POCT of biomarkers is limited to only plasma glucose [1]. In other regions ACs daily test for ketones, lactate and troponin. In the international setting the use of biomarkers in daily routine is well developed in some ambulance services and underdeveloped in other ambulance services [61].

2.6.1   suPAR

The biomarker soluble urokinase plasminogen activator receptor (suPAR) is the soluble form of the membrane bound protein uPAR, present on immunologically active cells. uPAR is released during inflammation or immune activation, and therefore suPAR levels reflect the extent of immune activation [62]. Elevated suPAR levels has been shown to be a sensitive and specific prognostic marker for bacteremia, sepsis, streptococcal pneumonia, septicaemia and myocardial infarction in the acute setting [63-65]. The biomarker suPAR is not applicable as a diagnostic marker [66]. It has also been established as a valuable marker to stratify mortality risk in the acute setting as well as in the ICU as it discriminates non-survivors from survivors across diseases [67-70]. In the general population, suPAR levels are higher in females than in males and increase with age. Lifestyle and risk factors, such as

smoking, physical inactivity and an unhealthy diet are associated with an increase in suPAR. Normal suPAR plasma level is 2-3ng/ml in healthy individuals, 3-4 ng/ml in unselected patients in the ED and above 9 ng/ml in critically ill patients [66]. Today, the quick test takes approximately 20 minutes and a quantifiable, a faster POCT is under development. However, despite its promise, there are still no studies demonstrating the added value of a suPAR test alone, or in combination with lactate measurements in the prehospital setting.

2.6.2 Lactate

Lactate is the base of lactic acid, first isolated in 1780 by Swedish chemist Scheele [71]. Lactate testing is standard procedure in Swedish EDs, but is more uncommon in the ambulance service. Lactate is not used within the ambulance service in Stockholm region. Under normal conditions, oxygen demand dictates oxygen delivery and is thus equal to oxygen consumption. A decrease in oxygen consumption while oxygen demand is unchanged denotes a state in which the delivery is inadequate to meet the demand, resulting in tissue hypoxia and tissue damage leading to organ dysfunction. The hypoxia in tissue is reflected by increased levels of lactate, which are related to the presence and severity of organ dysfunction [72-77] Elevated lactate levels have been shown to be more sensitive in identifying patients at risk of death than both systolic blood pressure and heart rate [78, 79]. Furthermore, lactate has been shown to be a predictor of negative outcome in the ED setting, both among patients with infections as well as those with non-infection-based conditions [80-82]. In summary, lactate can be used as a tool both with which to identify patients at risk and also as a tool with which to initiate treatment, both in the prehospital and the ED setting. However, the problem is that an increased lactate alone is not specific for sepsis or for any other condition.

3 RATIONALE

Non-specific chief complaints have over the latest decade emerged as one of the top five presenting complaints in the ED, often with vital signs within normal range. It has been established that as many as one third suffer a serious condition and increased risk of death. Meanwhile, because of the overall increase of patients assessed by both the ED and the ambulance service with a result of crowded EDs, there is a demand of differentiated levels of care.

However, our knowledge regarding ambulance service NSCs in general and the prevalence of serious conditions among those presenting with NSCs in particular is limited: this includes both the surveying and identification of serious conditions as well as the ACs experiences in caring for the patients presenting with NSCs. Increased knowledge from a quantitative and qualitative research perspective is needed to enhance patient safety.

4 RESEARCH AIMS

For patients with non-specific complaints in the pre-hospital setting; to describe the population for both those who are transported to hospitals or not i.e. conveyed or non-conveyed, to investigate whether biomarkers can contribute to the identification of those who develop a serious condition, and to describe the experiences of pre-hospital emergency nurses in caring for the patient.

Specific aims of the included studies:

Study I

The primary aim was to establish the prevalence of serious conditions among patients presenting to the EMS with NSCs. The secondary aim was to determine the mortality rates for patients presenting with NSCs.

Study II

The primary aim was to compare the prevalence of serious conditions among patients presenting with NSCs who were non-conveyed after the index EMS assessment and compared to those who were conveyed to an ED. The secondary aim was to compare mortality rates between these groups.

Study III

The aim was to explore PEN specialists' experiences in caring for patients presenting with NSC.

Study IV

The aim was to determine if suPAR and lactate could be used to identify serious conditions among patients presenting with NSCs to the EMS. The secondary aim was to describe the prognostic value for mortality in the group.

5 MATERIALS AND METHODS

The four studies in this thesis used, a quantitative approach (Studies I, II and IV) and a qualitative approach (Study III). An overview of the studies and methods is presented in Table 1.

Table 1: Overview of the design and methods used in the included studies

Study	Design	Study population/ Participants	Method for data collection	Method for analysis
Study I	Retrospective cohort	Adult (≥18 years) with NSC presenting to the ambulance service – conveyed (n=3780)	CAK-net (eHR), Patient register, Causes of death regisiter	Descriptive statistics Logistic regression
Study II	Retrospective cohort	Adult (≥18 years) with NSC presenting to the ambulance service – conveyed / non-conveyed (n= 4744)	CAK-net (eHR), Patient register, Causes of death regisiter	Descriptive statistics Logistic regression
Study III	Qualitative interview	Pre-hospital emergency nurses (n= 11)	Face to face interviews	Content analysis with inductive approach
Study IV	Prospective double blind observational cohort	Adult (≥18 years) with NSC presenting to the ambulance service (n= 414)	Blood samples in the ambulance CAK-net and TakeCare in Sweden Merlot Medi in Finland Study lab results	Descriptive statistics Logistic regression Likelihood analysis

5.1 Definition of serious condition

The definition of serious conditions established initially developed for ED purposes by Nemec et al. [21] was adapted to the EMS by "translating" the list of serious conditions into ICD-10 diagnosis codes including sub-codes. Chronic diagnoses and codes corresponding to non-acute diagnoses listed in the original Nemec et al. publication [21] were excluded from the list of ICD-10 diagnosis codes applied to the current EMS based study. Additional adaptations were made as follows: although neoplasms are by definition serious, neoplasms were not considered serious in the EMS context unless the patient was admitted to in-hospital care or died within 30 days of index EMS assessment. Infectious diseases were considered a serious condition if the patient was admitted to in-hospital care. The modified definition of serious condition was based on expert consensus, all of whom are senior emergency medicine- physicians with extensive prehospital experience or experienced emergency department and nurse specialists in prehospital care (Appendix 1).

5.2 Setting

5.2.1 Study I and II

Stockholm Region had a population of approximately 2.1 million (as of 2015). The Stockholm Region is responsible for operating the ambulance service and in this context relate to ambulance services. Ambulance service is provided by AISAB owned by the region [83], and two private companies [84, 85]. AISAB, performs approximately 42% of the total of 190 000 annual ambulance assignments in the Region. The Stockholm Region's ambulance assignments were distributed between 71 ambulances, 31 of which are operated by AISAB.

5.2.2 Study III

In Stockholm region, the regional regulations stipulate that at least one of the two ACs must be a registered nurse and must have completed an additional year of university training and hold a specialist nurse exam [3]. The specialist nurse is medically responsible within the ambulance team [1].

5.2.3 Study IV

The Pre-hospital Recognition and Identification of Unspecific Symptoms (PRIUS) study was initiated in May 2015 and completed in September 2017 and was carried out in Stockholm Region, Sweden and Uusimaa Region, Finland.

Stockholm Region had a population of approximately 2.1 million (year 2015). The Region was responsible for operating the ambulance service, and the service was provided by one organization within the region and two private companies. The ambulance service in Stockholm had almost 190,000 assignments in 2016. The number of ambulances in the area was 71 during the daytime and 40 during the night. All ambulances in Stockholm, Sweden were manned by a nurse specialist and an emergency medical technician (EMT).

The Uusimaa Region participating in the current study in Finland had a population of 480,000. The ambulance service in Uusimaa Region were organized by Helsinki University Hospital and provided by two fire departments and two private companies, operating 21 ambulances. The annual assignment rate was 50,000. In the Finnish ambulance service there are two levels of ambulances. Basic life support (BLS) units are staffed by two crew members with the minimum training requirement of vocational qualification in health care specialized in emergency care. The other member of the crew can be a health care professional (eg. a qualified nurse) or a fire fighter. In an Advanced life support (ALS) unit at least one of the crew must have a bachelor's degree in prehospital care or a degree in nursing with an additional specialization course in prehospital care. The other member of the crew can be either a health care professional or a fire fighter.

5.3   Participants and data collection

5.3.1 Study I and II

The NSCs were identified using the CAK-net eHR [86] used by the ambulance service. The ambulance medical record used in studies I and II constitute information on several patient demographic variables, including personal identification number, age, and gender. In addition to this, the record hold specific assignment information, such as assignment date, dispatch prioritization, assignment time variables, prehospital assessment information, observations, vital signs, administration of drugs, conveyance status and actions performed. Moreover, all ambulance medical records consist of a narrative text section written by the responsible AC. The narrative text section was excluded from the data extraction. The data obtained from

CAK-net was age, sex, vital signs at ambulance service triage, Glasgow Coma Scale [GCS], National Advisory Committee for Aeronautics [NACA] score, ambulance service disposition [conveyance to ED or non-conveyance].

The National Patient Register at Sweden's National Board of Health and Welfare is regulated by Swedish law and reporting to the register is mandatory. The register consists of patient demographic data, information on all in-patient, and out-patient care such as admission, discharge, length of stay, type of department admitted, referred to and discharged from as well as medical data, such as main – and secondary diagnosis, external cause of injury or poisoning and procedures. Data obtained from the National Patient Register was ICD-10 code at ED discharge, ED disposition [release to home or hospital admission], in-hospital length of stay [LOS], ICD-10 code from in-hospital discharge.

The Causes of Death register at the National Board of Health and Welfare is regulated by Swedish law and consist of information on all deceased individuals in Sweden and the causes of death reported by physicians, which is mandatory. Data obtained from the register was date of death.

The data obtained from the registers were compiled and anonymized in the final set of data in IBM SPSS Statistics for Windows, version 25 (IBM Corp. Armonk, New York, USA).

Triage levels were calculated retrospectively from vital signs from the index assessment by the ambulance service and based on RETTS and NEWS. The ESS were not included in the retrospective calculation of RETTS. The triage levels are indicated by color—blue, green, yellow, orange and red—with blue being the least urgent, and red the most urgent. RETTS' lowest level (blue) is not used by the ambulance service which makes the green level the least urgent in the ambulance service-setting. The NEWS scoring system is based on vital sign categories with the aggregated score converted to a three-level scale of clinical risk: low (0-4), medium (5-6) and high ($\geq$7) [56-58]. The Charlson comorbidity index (CCI) was calculated for each patient. All comorbid diseases not yet completely resolved were recorded [87].

Non-conveyance is defined as the decision not to transport the patient to the ED after EMS assessment. In Stockholm Region non-conveyance guidelines may be applied only if the patient is triaged to the lowest category in EMS, or refuses conveyance after assessment. Conveyance is defined as the patient being transported to an ED.

In Study I inclusion criteria were: all patients ≥ 18 years presenting with NSCs to the ambulance service delivered by AISAB, whose ambulance record contains a presenting complaint of "decreased general condition," "fatigue," "malaise" or "feeling unwell" according to the electronic health care record (eHR), and who were subsequently transported to an ED. The exclusion criteria were duplicated records, referrals, non-conveyance to an ED or patients deceased during the assignment (Figure 1).

Figure 1. Flowchart of inclusion and exclusion criteria in Study I

EMS: Emergency medical services; NSC: Non-specific chief complaint; MICU: Mobile Intensive Care Unit; NACA: National Advisory Committee for Aeronautics

In Study II inclusion criteria were: all patients ≥ 18 years presenting with NSCs to the ambulance service delivered by AISAB, whose ambulance record contains a presenting complaint of "decreased general condition," "fatigue," "malaise" or "feeling unwell" according to the electronic health care record (eHR), and who were subsequently conveyed to an ED or non-conveyed. The exclusion criteria were duplicated records, referrals or patients deceased during the assignment (Figure 2).
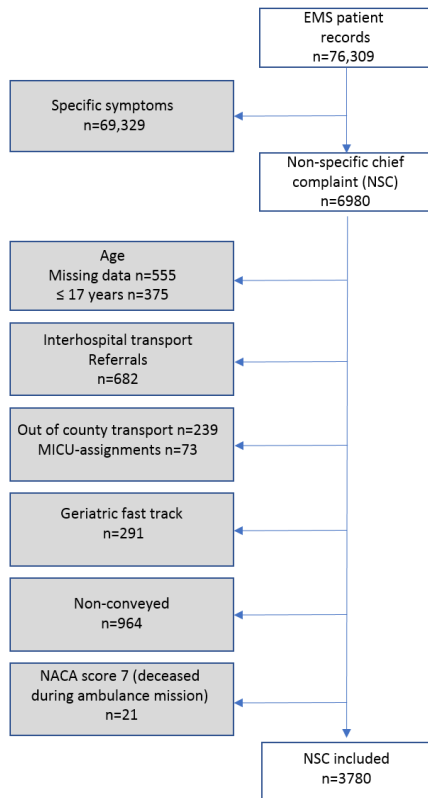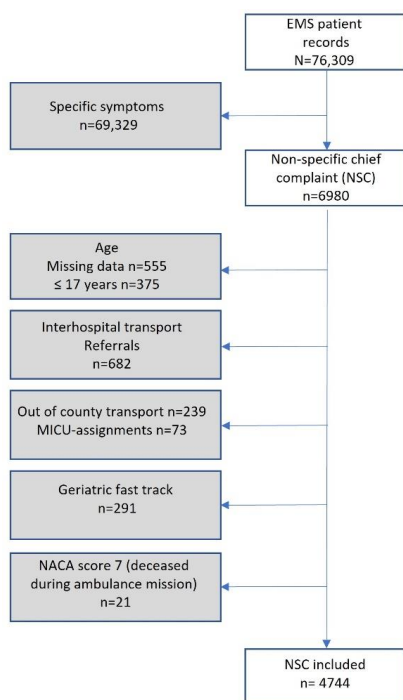
Figure 2. Flowchart of inclusion and exclusion criteria in Study II

EMS: Emergency medical services; NSC: Non-specific chief complaint; MICU: Mobile Intensive Care Unit; NACA: National Advisory Committee for Aeronautics

5.3.2 Study III

Data collection included a purposeful sample of PENs. Inclusion required that the participants were clinically active in the ambulance service in the Stockholm Region with a minimum of one year's experience as a PEN, lived experience of caring for patients presenting with non-specific chief complaints and consented to participate. The study was approved by the heads of department for all three ambulance companies, respectively, before the recruitment process of informants and data collection was initiated. Both written and verbal information was distributed among all three companies. A total of 11 ACs reported a willingness and approved to participate. Eight interviews were conducted in 2018 by two authors (JN and RSK) and an additional three in 2020 by the main author (RI) and were added to ensure data saturation. Interviews were performed at times and places chosen by the participants. The interviews lasted from 25 to 62 minutes (mean 35 minutes) and were recorded digitally, anonymized, and transcribed verbatim.

The interview began with an open question, "Can you tell me about your experiences in caring for patients with non-specific chief complaints?". The question prompted the

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informant to share experiences about the care of patients with non-specific chief complaints. The question was supplemented by follow-up and support questions such as "can you develop / tell more?", "how did you feel about it then?" and "can you tell me about a patient encounter?". The follow-up and support questions could vary between the interviews depending on how the informant responded and the purpose was to develop the informants' stories. They led to in-depth stories about informants' experiences, feelings and thoughts about the care of patients with non-specific chief complaints. Data collection continued until no new information was obtained from the interviews.

5.3.3 Study IV

In Study IV, patients presenting with NSCs to the ambulance service were included. The NSCs were defined as a presenting complaint of decreased general condition, fatigue, malaise, or feeling unwell upon ambulance service arrival. The inclusion criteria were NSCs, Swedish or Finnish personal identification number, being 18 years of age or above, informed consent by the patient or if personally unable, next-of-kin on behalf of the patient, transportation to an ED in Stockholm, Sweden or Helsinki Finland respectively, and normal vital signs, defined as: a heart rate of 50-100 beats/minute, oxygen saturation over 90%, systolic blood pressure over 100 mmHg, a respiratory rate of 10-25 raspirations/minute, body temperature of 36.0-38.5°C, and GCS 15. The exclusion criteria were not meeting inclusion criteria, and in the case of simultaneous specific complaints the patient was not eligible for inclusion.

After informed consent patients were enrolled in the study by the ACs, a peripheral venous cannula was inserted, and two blood samples were obtained before being transported to the ED. The samples were sent to the laboratory at the receiving hospital. All blood samples were centrifuged at the receiving laboratory within four hours. Lactate samples were analyzed continuously as a routine analysis, using an enzyme-based colorimetric assay (Roche Diagnostics Scandinavia AB, Solna, Sweden). Samples for suPAR were frozen and finally sent to the study lab where the samples were analyzed in batches using a commercial enzyme immunoassay (ViroGates, Birkeroed, Denmark). Electronic health records were obtained for all patients enrolled in the study from CAK-net and Take Care (CGM, Stockholm, Sweden) in Sweden and Merlot Medi (CGI Finland, Helsinki, Finland) in Finland. In-hospital patient data were obtained from electronic health records. The data collection included the following components for each patient: age, sex, vital signs at ambulance service triage, ED discharge diagnosis according to ICD-10, ED discharge disposition (home, admission to hospital), LOS

in hospital if admitted, discharge diagnosis (ICD-10), admission to in-hospital care, mortality (24 h and 30 days), and CCI, calculated by the researchers based on the patients' record data.

5.4 Analysis

5.4.1 Studies I and II

In study I and II descriptive statistics were used. The differences between groups were evaluated using Chi^2-test for the categorical variables, and Mann-Whitney U test for numerical variables. Logistic regression analyses were performed for the association of risk factors such as RETTS (Study I and II) and NEWS triage scores (Study I) with the presence of serious condition (primary outcome) and 24-hour, 30-day and in-hospital mortality (secondary outcomes). The lowest triage scores (RETTS green and NEWS low clinical risk) was separately analyzed. The results are presented as proportions and as odds ratios (OR) within a 95% confidence interval (CI). All statistical analysis was performed using IBM SPSS Statistics for Windows, version 25 in study I and version 27 in study II (IBM Corp. Armonk, New York, USA).

5.4.2 Study III

An inductive content analysis was carried out using the framework of preparation, organisation and presentation suggested by Elo and Kyngäs [88]. The analysis was performed in two separate sessions, where the first eight interviews were analyzed by three of the authors (RI, JN, RSK) and confirmed by two of the authors (KB, VV). After the addition of the three interviews in 2020, all eleven interviews were reanalysed by one author (RI) in the first round, by three authors (RI, VV, KB) in the second round and the rest of the authors (JN, RSK, LK and MC) in the final round. The analysis was based on three phases, preparation-, organizing- and, reporting phase. In the first phase, the preparation phase, the interviews were transcribed verbatim. The transcribed material was read repeatedly, to create a deeper understanding of the whole of what emerged in the interviews. In the second phase, the organizing phase, the collected material in the form of transcripts was divided into meaning-bearing units and organized by clustering the units into codes to identify similarities and discrepancies in the collected data. The codes were then sorted into broader sub-categories. This was done to get an overview of the different experiences that emerged in the texts that corresponded to the study aim. Subcategories were abstracted and merged into categories that

corresponded to aim of the study. In the third phase, the reporting phase, the results have been presented by sub-category, category and main category.

To ensure and preserve the essence of the reported experiences there was a continuous movement between the interviews, codes, sub-categories, categories and the main category. The continuous movement during the analysis was a systematic approach to account for the pre-understanding. Preunderstanding was managed by reflection and bridling. Prior to the data collection my preunderstanding was outlined and was a reminder during interviews and the analysis. Rather than excluding the preunderstanding, the bridling process controls it's impact on understanding of the data [89].

5.4.3 Study IV

In study IV descriptive statistics were used. Differences between groups are evaluated using a Chi^2-test and Fisher's exact test, where appropriate for the categorical variables, and Mann-Whitney U test for numerical variables.

Logistic regression analysis was performed to assess the association of risk factors with the primary outcome (presence of serious condition) and secondary outcome (24-hour and 30-day mortality). Area under receiver operating characteristics (AUROC) was calculated to assess the accuracy of the biomarkers tested. A prediction model was created and based on the biomarker, age and sex for absolute risk prediction. 2x2 contingency tables were used to calculate positive and negative likelihood ratios as well as positive predictive values (PPV) and negative predictive values (NPV) of the biomarkers on the outcome. Biomarker cut-off values were defined as: suPAR $\geq$3ng/ml, $\geq$6ng/ml, and $\geq$9 ng/ml, lactate $\geq$2.3 mmol/l. All statistical analysis was performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp. Armonk, New York, USA).

5.5 Ethical consideration

Research is an important part of healthcare development and the involvement of humans in clinical research necessitates substantial ethical reflection. All studies in this thesis were conducted according to the Code of Ethics of the Helsinki Declaration [90] and studies I, II and IV with the addition of the Code of Ethics of the Declaration of Taipei on health databases and biobanks [91].

Studies I and II were retrospective audits of registers and databases and did not include any intervention nor did it affect the treatment of the patients. However, a review of the register may be considered as a type of personal intrusion. The data was anonymized and stored locked in at the research center. All data was analyzed on group level and individuals could not be identified. The benefits of the studies were expected to exceed the possible harm associated with the review of personal data. In accordance with current procedures for implementing major registry studies in Sweden, informed consent was waived by the Ethical Review Board and was therefore not collected in Studies I and II. Ethical permission was obtained from the Stockholm Regional Ethical Review Board (Dnr. 2014/1999–31/4; 2016/1724–32).

In study III written informed consent was obtained, and all the informants received verbal and written information explaining the aim of the study, describing actions that would be taken to ensure the confidentiality of the participants. Furthermore, information about the participants' ability to withdraw their participation in the study whenever they wanted was provided. Following each interview, the recorded material was transcribed verbatim and transcribed data was stored electronically. The material has also been kept confidential, so that no unauthorized persons will have access to the material. Ethical permission was obtained from the Stockholm Regional Ethical Review Board (Dnr: 2016/727-31/5).

In study IV patients' medical records were accessed and blood tests were drawn. All invasive procedures, even drawing blood, are associated with a risk of complications such as infections. However, the risk of complications is low, and the ambulance service use point-of-care testing routinely (P-Glucose). The blood tests were not expected to have delayed the transport or affected the care of the patients. The possible benefits for future emergency care patients were considered to exceed the possible risks of the study procedure. All patients included in the study gave informed consent in person, and if personally unable, next-of-kin on behalf of the patient. If there was any uncertainty to whether the patient wanted to participate, the patient was excluded. All patients were informed of the possibilities in revoking the consent without any changes in the given care. The data was treated confidentially and was stored locked in at the research center. All data was analyzed on group level and individuals could not be identified. Ethical permission was obtained from the Stockholm Regional Ethical Review Board and the Operational Ethics Committee in Helsinki (Dnr: 2014/1999–31/4; 2016/1724–32; 2018/146-32 in Stockholm, Sweden; 329/13/03/02/2015 in Helsinki, Finland).

6 RESULTS

In this section, the main findings from each sub-study are presented. More detailed descriptions of the results are found in each of the studies placed at the end of this thesis.

6.1 Study I

The primary aim study I was to establish the prevalence of serious conditions among patients presenting to the EMS with NSCs. The secondary aim was to determine the mortality rates for patients presenting with NSCs.

A total of 3780 patients with NSCs were included with a median age of 77 years. Triage levels were: 60.8% ($n = 2027$) were green according to RETTS and 76.3% ($n = 2845$) had low clinical risk according to NEWS. 67.6% ($n = 2557$) of the patients were admitted to in-hospital care. The median in-hospital LOS was 5 days (range 0–72 days). Charlson Comorbidity Index median score was 1 point (range 0–9 points). A serious condition was present in 35.3% ($n = 1334$) of the patients presenting with NSCs. When a patient had a serious condition, a higher triage level according to both RETTS and NEWS was assigned, as compared to patients with no serious conditions. Overall, 4.2% ($n = 160$) of the patients died during the in-hospital care, 1.1% ($n = 42$) died within 24 hours, and 9.8% ($n = 372$) died within 30 days. In the group with serious conditions, 10.1% ($n = 135$) (OR 6.8, CI 95%, 4.1–11.3) died during in-hospital care, 1.9% ($n = 26$) died within 24 hours, and 20.2% ($n = 269$) (OR 3.1, CI 95%, 2.3–4.0) died within 30 days. In the group with no serious conditions 1.0% ($n = 25$) of the patients died during in-hospital care, 0.7% ($n = 16$) died within 24 hours and 4.2% ($n = 103$) died within 30 days. A serious condition was present in 23.9% ($n = 484$) of the patients triaged to RETTS green($n = 2027$), and 28.3% ($n = 804$) of the patients triaged to NEWS low clinical risk ($n = 2845$) (Table 2).

Table 2. Baseline characteristics for patients presenting with NSCs to the ambulance service

		Total N = 3780			Serious condition present n = 1334 (35.3%)			Serious condition not present n = 2446 (64.7%)			
		n	Md	(%)	n	Md	(%)	n	Md	(%)	p value.
Sex	Female	2033		(53.8)	682		(51.1)	1351		(55.2)	0.015
	Male	1747		(46.2)	652		(48.9)	1095		(44.8)	
Age			77			83			72		<0.001
	Missing	153		(4.0)	46		(3.4)	107		(4.4)	
RETTS	Green	2027		(60.8)	484		(40.7)	1543		(71.9)	<0.001
	Yellow	677		(20.3)	330		(27.8)	347		(16.2)	
	Orange	418		(12.5)	241		(20.3)	177		(8.2)	
	Red	214		(6.4)	134		(11.3)	80		(3.7)	
NEWS	Low risk	2845		(76.3)	804		(61.0)	2041		(84.7)	<0.001
	Medium risk	446		(12.0)	230		(17.5)	216		(9.0)	
	High risk	438		(11.7)	284		(21.5)	154		(6.4)	
CCI	Md		1			2			1		<0.001
Admitted	Yes	2557		(67.6)	1334		(100)	1223		(50)	<0.001
	No	1223		(32.4)	0		(0)	1223		(50)	
In-hospital LOS			5			6			3		<0.001
In-hospital mortality		160		(4.2)	135		(10.1)	25		(1.0)	<0.001
24 h mortality		42		(1.1)	26		(1.9)	16		(0.7)	<0.001
30 day mortality		372		(9.8)	269		(20.2)	103		(4.2)	<0.001

NSC: Non-specific chief complaint; RETTS: Rapid Emergency Triage and Treatment System; NEWS: national early warning score; CCI: Charlson comorbidity index; LOS: length of stay. Differences between serious conditions present/not present expressed as p-values.

In the group with serious conditions, 13.0% ($n = 63$) (OR 5.0, CI 95%, 3.2–7.9) of the patients in RETTS green, and 14.1% ($n = 113$) (OR 3.7, CI 95%, 2.7–7.9) of the patients in NEWS low clinical risk had died within 30 days. (Table 3).

Table 3. Logistic regression for serious conditions and mortality rates

			24h Mortality		In-hospital mortality		30-day mortality	
			OR	95% CI	OR	95% CI	OR	95% CI
RETTS Green	Serious condition	Yes	9.1*	1.0-78.3	15.6*	6.0-40.6	5.0*	3.2-7.9
		No	0.1*	0.0-1.0	0.1*	0.0-0.2	0.2	0.1-0.3
NEWS Low	Serious condition	Yes	3.0	0.9-10.0	10.5*	5.2-21.0	3.7*	2.7-7.9
clinical risk		No	0.3	0.1-1.1	0.1*	0.0-0.2	0.3*	0.1-0.3

*Regression model adjusted for sex, age, NEWS and RETTS. NEWS: national early warning score; RETTS-vs: Rapid Emergency Triage and Treatment System – vital signs. * p<0.05*

6.2 Study II

The primary aim was to compare the prevalence of serious conditions among patients presenting with NSCs who were non-conveyed after the index EMS assessment and compared to those who were conveyed to an ED. The secondary aim was to compare mortality rates between these groups.

A total of 4744 patients with NSCs were included in the study. Median age was 76 years of age. A serious condition was present in 29.5% ($n = 1398$) of the patients. The lowest triage according to RETTS was assigned to 69.1% ($n = 3278$) of the patients. When grouped by conveyance after index assessment by the ambulance service, 20.3% ($n = 964$) patients were non-conveyed. Among those, 6.6% ($n = 64$) had prevalent serious conditions compared to 35.3% ($n = 1334$)(OR 4.8, CI 95% 3.6-6.4) patients in the conveyance group (Table 4 and 5).

Table 4. Baseline characteristics for patients presenting with NSCs to the ambulance service grouped by conveyence

		CONVEYED									NON-CONVEYED								
		Total			Serious condition present			Serious condition not present			Total			Serious condition present			Serious condition not present		
		n = 3780			n = 1334 (35.3%)			n = 2446			n = 964			n = 64 (6.6%)			n = 900		
		n	Md	(%)	n	Md	(%)	n	Md	(%)	n	Md	(%)	n	Md	(%)	n	Md	(%)
Sex	Female	2033		53.8	682		51.1	1351		55.2	531		55.1	34		53.1	497		55.2
	Male	1747		46.2	652		48.9	1095		44.8	433		44.9	30		46.9	403		44.8
Age			77			83			72			69			83			67	
Time of day	07.00-14.59	1885		50.2	746		56.3	1139		46.9	312		32.7	29		45.3	283		31.8
	15.00-22.59	1319		35.1	461		34.8	858		35.3	367		38.4	22		34.4	345		38.7
	23.00-06.59	552		14.7	118		8.9	434		17.9	276		28.9	13		20.3	263		29.5
Priority outbound	1	1423		37.6	463		34.7	960		39.2	413		42.8	22		34.4	391		43.4
	2	1870		49.5	675		50.6	1195		48.9	437		45.3	34		53.1	403		44.8
	3	487		12.9	196		14.7	291		11.9	114		11.8	8		12.5	106		11.8
Priority inbound	1	412		10.9	235		17.6	177		7.2	-	-	-	-	-	-	-	-	-
	2	1804		47.7	644		48.3	1160		47.4	-	-	-	-	-	-	-	-	-
	3	1564		41.4	455		34.1	1109		45.3	-	-	-	-	-	-	-	-	-
RETTS	Green	2368		62.6	586		43.9	1782		72.9	910		94.4	57		89.1	853		94.8
	Yellow	734		19.4	348		26.1	386		15.8	39		4.0	3		4.7	36		4.0
	Orange	452		12.0	259		19.4	193		7.9	10		1.0	3		4.7	7		0.8
	Red	226		6.0	141		10.6	85		3.5	5		0.5	1		1.6	4		0.4
CCI	Md		1			2			1			1			2			1	
Admitted	Yes	2557		67.6	1334		100	1223		50	-	-	-	-	-	-	-	-	-
	No	1223		32.4	0		0	1223		50	-	-	-	-	-	-	-	-	-
24 h mortality		42		1.1	26		1.9	16		0.7	5		0.5	1		1.6	4		0.4
30 day mortality		372		9.8	269		20.2	103		4.2	32		3.3	11		17.2	21		2.3

NSC: Non-specific chief complaint; RETTS: Rapid Emergency Triage and Treatment System; CCI: Charlson comorbidity index.

In the conveyance group, 30-day mortality was 9.8% ($n = 372$)(OR 1.7, CI 95% 1.1-2.7) compared to 3.3% ($n = 32$)(OR 0.6, CI 95% 0.4-0.9) in the non-conveyance group. In the conveyance group without prevalent serious conditions 30-day mortality was 4.2% ($n = 103$)(OR 1.7, CI 95% 1.1-2,7). For the non-conveyance group without prevalent serious conditions, 30-day mortality was 2.3% ($n = 21$)(OR 0.6, CI 95% 0.4-0.9) (Table 4 and 5).

Table 5. Logistic regression for serious condition and mortality rates

		Serious condition		24h Mortality		30-day mortality	
		OR	95% CI	OR	95% CI	OR	95% CI
Conveyed	Yes	4.8*	3.6-6.4	2.6	0.6-11.4	1.7*	1.1-2.7
	No	0.2*	0.2-0.3	0.4	0.1-1.7	0.6*	0.4-0.9

*Regression model adjusted for sex and age. * p < 0.05*

6.3   Study III

The aim of study III was to explore PEN specialists' experiences in caring for patients presenting with NSC.

The exploration of pre-hospital emergency nurse specialists' experiences in caring for patients presenting with non-specific chief complaints resulted in one main category '*In-depth systematic assessment is perceived to reduce suffering and increases patient safety'*. It illustrates the importance of a systematic assessment done by the PEN to alleviate the suffering in patients and to promote more patient safety when encountering the patient with non-specific chief complaints. It is important to keep the patient in focus to create an important meeting. The PENs described how they assessed the lack of specific symptoms, the patient history, and the living environment to create a comprehensive picture of what the patients was experiencing and to exclude different conditions. Knowledge and experience are highlighted as vital for achieving good and safe care. PENs emphasized the importance of feedback on assessments and given care to develop their own competence, as the assessments of patients presenting with NSCs was perceived as requiring a higher level of competence.

The main category was founded on three categories;

(1) Unexplained suffering was experienced by the participants that the caring encounters with patients presenting with NSCs are complex, and they struggle to find a reason for the suffering the patient tries to express. The information obtained from next of kin or related parties is considered of great importance for the continued assessment of the patient.

(2) Systematic approach and experience enhance medical safety is based on feelings of uncertainty and inadequacy that may arise when encountering the patients presenting with NSCs due to absence of specific symptoms. Those feelings can be managed by the utilization of a systematic approach while assessing the patient. The knowledge based on experience was a contributing factor towards a perception of increased patient safety and more accurate assessments.

(3) Organizational processes can be optimized showed that the perceived complexity of patients presenting with NSCs places higher demands on PENs competence to meet the patient's needs. The lack of differentiated levels of care is challenging for the participants and is perceived to impair patient safety. It was also found that a lack of feedback increases the risk of hampering the continuing knowledge development of PENs.

6.4   Study IV

The aim study IV was to determine if suPAR and lactate could be used to identify serious conditions among patients presenting with NSCs to EMS. The secondary aim was to describe the prognostic value for mortality in the group.

A total of 414 patients were included. The median age was 82 (IQR 75–88) years of age. Female patientens represented 56.5% ($n = 234$) of these. 55.1% ($n = 225$) of the patients were admitted to in-hospital care. The median in-hospital LOS was 3 days (IQR 0–9). A serious condition was present in 15.2% ($n = 63$) of the included patients. The absolute risk for having a serious condition was at the highest at 34.9% for men older than 80 years and having a suPAR above 9 ng/ml. Overall, 4.1% ($n = 17$) of the patients died within 30 days. In the group with serious conditions, 9.5% ($n = 6$) of the patients died within 30days, compared to 3.1% ($n = 11$) in the group with no serious conditions (Table 6).

Table 6. Patient characteristics and outcome

		Total			Serious condition present			Serious condition not present		
		N = 414			n = 63 (15.2%)			n = 351 (84.8%)		
		n	Md (IQR)	(%)	n	Md (IQR)	(%)	N	Md (IQR)	(%)
Sex	Female	234		(56.5)	34		(54.0)	200		(57.0)
	Male	180		(43.5)	29		(46.0)	151		(43.0)
Age	Md		82 (75-88)			85 (79-90)			81 (75-88)	
Admitted	Yes	225		(54.3)	54		(85.7)	171		(48.7)
	No	189		(45.7)	9		(14.3)	180		(51.3)
In-hospital LOS			2 (0-9)			8 (3-13)			1 (0-7)	
CCI			2 (0-9)			1 (0-2)			1 (0-7)	
24 h mortality		0		(0.0)	0		(0.0)	0		(0.0)
30 day mortality		17		(4.1)	6		(9.5)	11		(3.1)

Md: median; IQR: interquartile range; LOS: length of stay. CCI: Charlson comorbidity index.

The area under receiver operating characteristics (AUROC) for having a serious condition was 0.63 (95% CI 0.56–0.70), $p < 0.001$ for suPAR and 0.46 (95% CI 0.39–0.53), $p = 0.30$ for lactate (Figure 3a). The AUROC for 30-day mortality was 0.78 (95% CI 0.65–0.91), $p < 0.001$ for suPAR and 0.62 (95% CI 0.48–0.77), $p = 0.09$ for lactate and (Figure 3b).

3a

3b
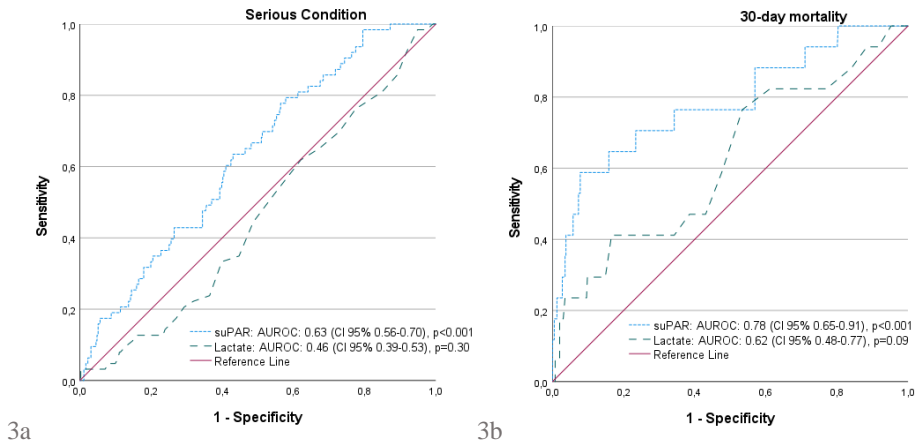
Figure 3a: ROC curve based on suPAR and lactate by prevalent serious condition. 3b: ROC curve based on suPAR and lactate by 30-day mortality.

A positive likelihood ratio (LR+) of 1.17 and a positive predictive value (PPV) of 17.3% as being predictive of a serious condition was observed when suPAR was elevated above 3 ng/ml. A LR+ of 4.67 and a PPV of 16.7% was observed for suPAR levels above 9 ng/ml as being predictive of 30-day mortality. Lactate was not significantly predictive of serious conditions or 30-day mortality (Table 7).

Table 7. Predictive ability and likelihood ratios of soluble urokinase plasminogen activator receptor (suPAR) and lactate with respect to serious conditions and 30-day mortality. P value <0.05 is considered significant.

		Serious condition n=414					30 day mortality n=414				
		PPV	*NPV*	*+LR*	*-LR*	*sig.*	*PPV*	*NPV*	*+LR*	*-LR*	*sig.*
suPAR	≥3 ng/ml	17.3%	98.2%	*1.17*	*0.0*	*p<0.001*	4.7%	100%	*1.16*	*0.0*	*p=0.145*
	≥6 ng/ml	19.0%	86.8%	*1.31*	*0.91*	*p=0.08*	8.5%	98.2%	*2.16*	*0.43*	*p=0.03*
	≥9 ng/ml	21.7%	85.9%	*1.54*	*0.92*	*p=0.171*	16.7%	98.0%	*4.67*	*0.47*	*p<0.001*
Lactate	≥2.3	11.2%	83.2%	*0.70*	*1.12*	*p=0.173*	6.0%	96.8%	*1.5*	*0.81*	*p=0.269*

PPV: positive predictive value; NPV: negative predictive value; +LR: positive likelihood ratio; -LR: negative likelihood ratio

7 DISCUSSION

The overall aim of this thesis was for patients with non-specific complaints in the pre-hospital setting; to describe the population for both those who are transported to hospitals or not, to investigate whether biomarkers can contribute to the identification of those who develop a serious condition, and to describe the experiences of pre-hospital emergency nurses in caring for the patient.

The results indicate that NSCs represent a non-negligible part of the ambulance assignments. Among those presenting with NSCs to the ambulance service, one third of the patients had serious conditions. The patients were generally older and serious conditions were associated with increased mortality rates. Biomarkers tested have been found not to contribute to the identification of serious conditions. Patients who were non-conveyed had fewer serious conditions compared to those transported to the ED. Prehospital emergency nurses' experiences show a complex assessment situation, where they struggle to identify the cause of NSCs and must conduct the assessment with a systematic approach to maintain the patients' best interests in focus. Lacking organizational factors contribute to the feelings of frustration and inadequacy and can furthermore complicate the person-centered focus.

7.1 Non-specific chief complaints

NSCs continue to be fairly unexplored in emergency medicine in general and pre-hospital emergency care in particular. Displayed as "all complaints that are not part of the set of specific complaints or signs or where an initial working diagnosis cannot be definitively established" [21], NSCs cover a broad set of complaints. Being one of the top five ED presentations, make NSCs a non-negligible complaint in the whole chain of emergency medicine, from the EMCC to the in-hospital care [5, 21, 27]. In a Danish cohort, it was found that a substantial number of patients were diagnosed with non-specific diagnoses, such as "unspecified disease" and "observation for disease" [92]. That in combination with the previous knowledge of the risk of misdiagnosis [36-39, 93] further strengthens the hypothesis that the identification of disease is complicated when presented with NSCs. National, and regional ambulance service guidelines in general and Stockholm in particular, are lacking regarding patients presenting with NSCs. The guidelines are designed from specific chief complaints and specific symptoms. Guiding information is scarce. In a few there is a desire to avoid the NSCs as primary assessment classification if possible. The goal in the guidelines is

to strive for and to maintain stable vital signs. The registered AC, e.g., registered nurse is responsible for the assessment and further contact with the physician on call for further guidance regarding level of care.

7.2 Serious conditions

The lack of a universal definition of serious conditions may complicate both the outcome-based research and evaluation of clinical performance. A narrow, disease-specific endpoint definition for serious conditions is not suitable due to the broad spectrum of possible diseases underlying a NSC presentation. The definition may be more suitably build on distinguishing between serious and non-serious conditions. According to Chrvala and Sharfstein [94] a number of criteria could be used to describe serious conditions, including severity of illness, degree of impairment, and the level of need for comprehensive care management. These conditions may be serious and complex for some patients at some points during the course of their disease or disability, but not necessarily always serious and complex for all patients. Nemec et al [21] defined a serious condition as "any potentially life-threatening condition (as exemplified by a myocardial infarction) or any condition that requires an early intervention to prevent health status deterioration leading to possible morbidity, disability, or death (as exemplified by severe hyponatremia)". They further defined "any death occurring within 30 days of the initial ED presentation as being due to a serious condition, even in cases for which the exact serious condition could not be definitively identified". Karakoumis et al [31] further defined the serious conditions as "acute morbidity was defined as a serious condition, that is, any condition requiring early intervention (eg the use of antibiotics) to avoid deterioration of health status, possibly leading to adverse health outcomes such as disability, or death".

In this thesis and the studies I, II and IV, a definition of serious conditions was formulated by adopting the definition initially developed for ED purposes by Nemec et al [21]. The list was adapted to the ambulance service by "translating" the list of serious conditions into ICD-10 diagnosis codes, including sub-codes. The Swedish National Board for Health and Welfare's National Patient Register is based on registered ICD-10 codes and not the assessed conditions by ambulance service clinicians. Therefore, it was necessary to translate the list of serious conditions into ICD-10 codes. Since conditions may have both acute and chronic components as well as being taken care of in primary care, we chose admission to in-hospital care as a proxy for a condition to be "serious" in some of the listed conditions. Our definition of

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serious conditions and their translation into ICD-10 codes may be more precisely transferrable in future research.

Serious conditions were present in up to one in three patients in study I and II, and one in six in study IV. The lower proportion in study IV can be explained by the inclusion criteria withheld only vital signs within the normal reference range, choosing only the equivalent of RETTS green. In the sub analyses of studies I and II, up to one in four patients had present serious conditions when triaged to RETTS green. Compared to approximately 60% in prior studies in ED settings [21, 31, 95]. It is surprising, since patients arriving to the ED by ambulance are in general sicker than those who "walk in" [96]. The conflicting finds may partly be explained by the definition of serious conditions used in studies I, II, IV and this thesis, since it may select for a sicker population. Despite the differences, the prevalence of serious conditions is high. Interestingly, even among patients triaged to low triage scores. This implies that vital sign-based triage scores are an insufficient tool with which to identify serious conditions.

The most common discharge diagnosis in studies I and II was an infectious disease, such as pneumonia or urinary tract infection. The infectious diseases were followed by cardiovascular and neurological diseases. The findings are in line with previous studies of elderly patients presenting to the ED with NSCs [97], and that infections are the main complaint of elderly non-trauma ED patients [23].

7.3   Age

A majority of the patients in studies I, II and IV were old, with a high median age. Previous studied have established that the elderly are frequent users of the ED, due to the ageing of the population and the increase of prevalence of chronic-degenerative diseases, predisposed to frequent exacerbations. Elderly patients represent around half of the ambulance assignments and ED visits [5, 32, 98-100]. The atypical symptom presentation may also be complicated by comorbidities and polypharmacy. One partial explanation to the atypical symptoms, or NSCs, are the dysregulated organ system functions. The dysregulation is a result of age-associated pathophysiology and age-related loss of protective homeostatic mechanisms, suggesting that the vital sign response may remain within normal reference intervals, and is unable to respond appropriately to stressors, such as disease and inflammation[101-106]. Vital signs are commonly considered as a universal communication tool for patient status and severity of illness, and can when deranged, alert the clinician to a disease process and severity

but cannot define the ongoing disease process. However, when within normal reference interval, the vital signs provide near to none information unless a known baseline is present. With a baseline and successive measurements, adverse events may be avoided [101]. In studies I and II most of the patients were triaged to low RETTS scores, and in study IV all patients were triaged to a low RETTS score. With the knowledge on physiologic age-related changes, it can be argued that the measurement of vital signs in the ambulance may be insufficient decision-making-support tools without an established baseline. In many cases such baseline information is inaccessible and not known for the ACs. Therefore, study IV aimed to evaluate the two biomarkers as prognostic tools as an objective addition to the well-established vital signs-based assessments.

7.4 Mortality

In study I the 30-day mortality rate was as high as one in five when a serious condition was present. In study II one out of six died within 30 days when a serious condition was present. In study IV the corresponding number was one in ten. In all three studies mortality rates were higher in the group with serious conditions compared to those with no serious conditions. The mortality rates were higher than in the study by Nemec et al [21] and Karakoumis et al [31], lower than Säfwenberg et al [5] and Wallgren et al [107]. Patients with green triage levels were analyzed separately enabling comparison across studies I, II and IV. The 30-day mortality rates were then comparable in cases with present serious conditions. Similar 30-day mortality rates were presented by Wachelder et al [108], who also found that NSCs had an increased mortality risk when compared to those presenting with specific complaints.

Since patients presenting with NSCs also have higher mortality rates, it can be discussed if the NSCs or high age could be an indicator for death in the near future, or if the presence of serious conditions is the true indicator. The patients presenting with NSCs and high age, and who did not have serious conditions had much lower mortality rates, which could contradict the first hypothesis in favor of the latter.

In study IV the biomarker suPAR was shown to be associated with mortality. Elevated suPAR was predictive for mortality and could be an indicator for further medical assessment and risk stratification.

7.5 Pen experiences

In study III the experiences of PENs in caring for patients presenting with NSCs were explored. This group of patients is perceived as challenging and patient safety is considered important. The first category *unexplained suffering* was perceived as a barrier, as PENs try to identify the cause of the suffering. Next-of-kin or other care givers as a source of information, when possible, was one way of trying to identify the cause, since the patients themselves many times could not describe the complaint. Patience and taking the time needed, when assessing the patient emerged as important. Time to get to know the patient and the suffering they experience and involving them in the care is key [14]. The second category *systematic approach and experience enhances medical safety* is based on feelings of uncertainty and inadequacy that may arise when encountering the patients presenting with NSCs. The fear of missing something that could cause more suffering and discomfort for the patient is in line with previous publications [109]. To avoid missing something important the PENs expressed that systematic assessment were key in trying to find the cause of the suffering and the appropriate level of care. The systematics were described as a kind of detective work, with attention to detail and extending the focus from the physical assessment to the living environment. The encounter was perceived as laying out a puzzle, where every bit of information was a piece of that puzzle. The ability to collect and lay more pieces of the puzzle was perceived dependent of clinical experience and gestalt. In the third category *organizational processes can be optimized* PENs tell of experiences in their working environment which they have little to no mandate to change. A key task for the PENs is to protect the patient's best interests [110]. Still PENs felt that many patients care was limited by conveyance to the ED, when geriatric wards lacked beds or when primary care centers were closed, which did not benefit the patient's best. This limitation results in conveyance to the ED, even if it is not perceived as the best solution for the individual patient. PENs desired receiving feedback on the given care and the patient's outcome as a significant part of knowledge development. According to Wihlborg et al. [111], daily feedback, was sought after and considered to be crucial for skills development. There is a need for confirmation of whether the assessment was correct. Without feedback there is a risk that patients could be incorrectly assessed on a continuous basis[112]. The main category, *in-depth systematic assessment is perceived to reduce suffering and increases patient safety*, PENs experiences could be summed as applying in-depth systematic assessments with the intention to reduce the risk of missing important and vital information whilst maintaining the patient centered approach. The systematic approach may also aid the less experienced PENs in their assessment of the patient in general, and the patient presenting with NSCs in particular. The

desired feedback is on an organizational level and could enhance the knowledge development on an individual level, as well as group levels.

7.6 Adequate assessments

Assessing patients presenting with NSCs is still a challenging task, with many pitfalls of risk for missing those with serious conditions not yet specifically symptomatic. Identification of serious condition is still not possible by the objective tools in the ambulance. Study I explored the prevalence of serious conditions among patients presenting with NSCs to the ambulance service. It indicated that vital signs were an insufficient tool with which to identify the serious conditions. The triage system RETTS ESS code 53 covers the NSCs, differentiating the patients defined by time of onset of symptoms, mental status and immunosuppression as follows in descending order; orange: acute onset and/or immunosuppression, yellow: subacute onset and/or deviant behavior, green: none of the above. No further guidance is given when assessed as NSC [1, 55, 113]. In study II the result show that fewer patients who are non-conveyed had serious conditions when compared to those who are conveyed to the ED. The findings indicate that most patients are assessed adequately, and the level of care could be appropriate. Nevertheless, knowledge regarding non-conveyance is limited and lacking a uniformed definition [114]. NSCs, and vital signs within the reference interval of normal, being one of the factors in non-conveyance have been established previously [115-119]. One worrying aspect is that a small proportion of the non-conveyed patients' in study II, had serious conditions and were hospitalized within seven days. Similar findings are presented by Magnusson et al [119] where a majority of non-conveyed patients who were hospitalized within 72 hours presented with NSCs. Similar findings were reported in a Dutch study [120]. In study II, the patients were elderly, and with the knowledge on physiologic age-related changes and due to the non-conveyance decision being based on low triage scores, it can be argued that the measurement of vital signs in the ambulance may be insufficient decision-making-support tool without an established baseline based on previously repeated measurements. In many cases such baseline information is inaccessible and not known for the ACs [23, 31, 101]. Nevertheless, the findings are an indication that the assessment and decision for non-conveyance may be adequate and are based on variables not measured in the studies included in this thesis. Study III indicates that the systematic approach, experience-based knowledge and considering more aspects of the patient's situation, such as living environment and information from next-of-kin or other caregivers

could give a more adequate assessment of the patient than vital signs and guidelines. The findings are supported by theoretical models of clinical reasoning, where the dual-processing theory features two systems of thinking [121-124]. The two systems, the intuitive and the analytical build upon generating multiple hypotheses in the first, while gathering information from multiple sources and consciously weighting the information aligns with the latter. The aforementioned fear of missing important information, leading to adverse events and eventual harm for the patient may also be described as the risk of diagnostic errors in clinical reasoning, from cognitive biases to knowledge deficits. Knowledge in the two systems of clinical reasoning may aid, both the individual ACs and the organization, in avoiding and controlling the risk of error. The intuitive system associates between the new information and similar examples from one's memory. The retrieval of similar examples is related to the strength of the association, i.e., the number of previous observations and common features. The analytical system is consistent with logical rules, and the processing of knowledge [125]. Taking the time needed may reduce the intuitive system errors, by invoking the analytical system [126]. If the errors are a consequence of knowledge deficits, then more experience will lead to greater knowledge, both analytical and experiential and may in that case result in fewer errors. Specific knowledge can correct the risk of errors when applied [125]. These strategies may reduce the risk of error if applied to the findings in study III, where the desired feedback for knowledge development is lacking. Lederman et al [127] found that the lack of feedback on given care complicates knowledge development, creating a feedback paradox, where ACs base parts of their assessments on experience-based knowledge, which is line with the theoretical knowledge in clinical reasoning.

8 METHODOLOGICAL CONSIDERATIONS

8.1 Research methods

Different research methods were used in this thesis. To explore the prevalence of serious conditions and mortality among patients presenting with NSCs, both those who were conveyed and those non-conveyed (Studies I and II) a retrospective cohort study with descriptive analysis was used. To explore the experiences of PENs in caring for patients presenting with NSCs (Study III), a interview study with a inductive qualitative content analysis according to Elo & Kyngäs [88] was used. To determine the abilities in identifying serious conditions and the prognostic value of biomarkers among patients presenting with

NSCs (Study IV), a prospective, double blind, observational study was conducted. With the aims in mind, the methods used in the four studies were deemed appropriate.

8.2   Lack of definitions

The definition of NSCs can be discussed controversially [128]. To our knowledge there is no universal definition, and different nomenclatures have been used in the past, such as decreased general health condition, unexplained symptoms, general disability, and atypical symptoms. Not many studies have been published on NSCs, and even those are heterogenous. This diversity has not been helpful for a clinical definition or research on NSCs [27]. There is a consensus that studies are needed to form a common definition, to improve the quality of future research [129-131].

The lack of a universal definition of serious conditions may complicate both the outcome-based research and evaluation of clinical performance. Therefore, we chose to modify a previous definition, originally defined by Nemec et al [21]. Our definition of serious conditions and their translation into ICD-10 codes may be more precisely transferrable in future research (Appendix 1).

8.3   Biomarkers

ACs daily encounter patients with a range of complexity and who are suffering from acute pathologies. ACs face these scenarios with very limited objective diagnostic information, which could hamper their clinical decisions. Different early warning biomarkers have been developed in the last years with some of them already encompassed into the common clinical practices in the ED. Some of these are available as POCT, which is considered as obligatory in the prehospital context. The biomarkers studied in study IV are both available as POCT. In study IV, the test was not analyzed as POCT, but instead sent to the laboratory in the receiving hospitals. The analysis of the biomarkers was considered reliable. Test reliability refers to the degree to which a test is consistent and stable in measuring what it is intended to measure. suPAR levels in healthy individuals are known to be stable throughout the day [132] and are not affected by repeated freeze-thaw procedures, or being stored in room temperature up to 24 hours [133]. The decision of data collection method was based on cost-effectiveness on one hand, and foremost the double-blind approach on the other hand. If not

blinded, suPAR and lactate results could potentially have affected the ACs and/or hospital staff into assessments based on the biomarkers, even though their significance and predictive values were not yet evaluated.

8.4   Register based data

There are both advantages and challenges when conducting research based on existing registers (Studies I and II). Retrospective data collection is time-efficient, cost-effective and often reproducible [134]. One of the main challenges is the validity of the register, and knowledge of the data quality is necessary to assess the validity and to increase generalizability [135]. The electronic ambulance medical records used in study I, II and IV were not created for research purposes, but are considered as local eHR. Data retrieved from the eHR was predefined variables, imported in the pooled database used for analysis. The patients were identified via the ambulance eHR which made it challenging to extract patient data based on assessment classifications (Studies I and II). This due to the ability of ACs to document patients with NSCs using different assessment categories may have led to some patients being excluded from the data. Despite this, the size of the current cohort is relatively large, and the results therefore considered to be generalizable. The National Patient Register administered by the Swedish National Board of Health and Welfare is considered valid and reliable.

The lack of definitions of NSCs may affect the way ACs document the assessment of the patient's complaints. They could choose to refrain from the predefined 140 prehospital initial assessment categories and use a narrative description. In cases where no categories had been used, the patient was impossible to identify and was thus missed. The data analyzed was quantifiable and measured, which may have been inadequate for answering the questions, "Why" and "How" the patient was assessed as NSC. However, the data available, was sufficient to answer the questions formulated in the aims of the studies I and II. Unfortunately, EMCC categorization was not included in our data, hence excluding information from an important part of the prehospital emergency medical chain. Such information would be of interest when trying to capture the whole picture of the NSC assessment.

In studies I and II, data was extracted from only one of the three companies in the ambulance service in Stockholm region. Performing approximately 40% of the ambulance assignments in the region, one could argue that the selection of patients could be biased. AISAB operates

in different parts of the region, covering densely populated areas to more rural areas and different socioeconomic characteristics ranging from low socioeconomic status to the highest possible within the catchment area. The population assessed by AISAB ACs represent the expected cross section of a nation's capital.

8.5   Qualitative approach

The content analysis in Study III, was conducted in order to create an inductive approach [88]. Hence, a qualitative content analysis was judged compatible with the aims and the level of data. When there is a limited amount of research in a chosen field, it is considered that the inductive approach can be seen as an advantage as in the current study. However, one disadvantage of the inductive approach may be that the understanding does not increase or that the phenomenon studied is not explained [88]. A purposeful sample was considered appropriate for this study. According to Elo et al. [136], the selection of participants based on purposeful sampling, produces adequate data if there is something specific that is being investigated. Through purposeful sampling, a number of individuals are selected who are assumed to possess relevant knowledge and experiences about the subject, as well as being able to provide ample descriptions that answer the purpose [137]. Trustworthiness was established by producing open and unstructured data via interviews with open-ended questions. To facilitate and ensure dependability the interviews were conducted by three of the authors using the same opening question and follow-up questions. Data analysis was initially performed by three of the authors (RI, JS, RSK) and reanalyzed by three of the authors (RI, VV, KB). The other authors confirmed the analysis. During the analysis, discussions took place until consensus was achieved aiming to formulate internal homogenous and external heterogenous categories, in order to achieve trustworthiness [136]. Quotations were used to further strengthen the trustworthiness [138, 139]. An on-going discussion and reflection upon our pre-understanding was maintained by critical discussion prior and during the interviews and analysis, in order to enhance the credibility of the study.

Transferability refers to the extent to which the findings of a study can be transferred to other contexts or groups [138, 140]. Swedish ambulance care differs from other countries with regard to the ACs profession. However, the patients are similar and the objective, responding and assessing patients with different conditions in general and NSCs in particular. The results in study III can have meaning in other countries and systems, as well as other contexts, such as EDs and primary care.

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9 CONCLUSIONS

This thesis has shown that serious conditions are present in approximately one third of the patients presenting with NSCs to the ambulance service, which is a non-negligible proportion. Patients presenting with serious conditions while presenting with NSCs have increased mortality rates. However, non-conveyed patients presenting with NSCs to the ambulance service had lower proportions of serious conditions, despite no differences could be noted in the objective findings when compared to those transported to the ED. The use of the biomarkers suPAR and lactate have shown ineffective in identifying serious conditions, but elevated suPAR was associated with increased mortality and could be an indicator for further assessment and risk stratification. PENs experiences in caring for the patients presenting with NSCs show that in-depth systematic assessment is perceived to reduce suffering and increases patient safety. Patients have a perceived unexplained suffering, which can be addressed by keeping the patient in focus while creating a meaningful encounter. Experience and a systematic approach are considered key to enhance medical safety. Organizational processes could be optimized to allow feedback on given care to increase knowledge and professional development as well as a wider range of options on the level of care the patient could be conveyed to.

Identification of serious conditions among patients presenting with NSCs to the ambulance service remains a challenge. Increased education and feedback on given care would likely increase the identification. However, an enhanced understanding of the atypical presentations of NSCs and the process of clinical reasoning could strengthen the ACs in performing person-centered care.

10 POINTS OF PERSPECTIVE

10.1 Clinical implications

The findings and conclusions in this thesis could have clinical implications and the following list is a suggestion as how to use the knowledge generated by this thesis.

- Increased knowledge and awareness of the group of patients presenting with NSCs to the ambulance service.
- Increased knowledge on the presence of serious conditions among patients presenting with NSCs to the ambulance service and the increased mortality in the group.
- Increased awareness of the possible pitfalls of vital sign based triage systems, both in being unable to differentiate between presence and absence of serious conditions as well as on a organizational level when formulating medical guidelines for the ambulance service.
- Identification of important aspects in the assessment of patients presenting with NSCs to the ambulance service that need organizational support, education efforts, allowing feedback on given care to enhance knowledge and professional development.

10.2 Future research

Several questions and ideas for future research emerged during this work:

- To explore the prevalence of occult hypoperfusion among patients presenting with NSCs and the association with serious conditions.
- To explore the experiences of PENs on the care of frail elderly patients presenting with NSCs to the ambulance service.
- Development of a universal definition of NSCs to ensure the homogenity of future research.
- To explore how ambulance service guidelines formulate on patients presenting with NSCs, and further explore the experiences of the those responsible for formulating the guideline regarding the clinical reasoning in the guideline.
- Research that explores and validates the reference intervals of vital signs in the elderly patient.
- Prospective research on assessment and reassessment of patients presenting with NSCs who are non-conveyed or patients in perceived need of different levels of care other than ED,

where patients are reassessed within 12 hours by the EMCC physician on call via telephone, generating a recommended assessment, either by ambulance or referral to primary care.

- To describe words, expressions and patterns during the emergency call for patients presenting with non-specific chief complaints to the ambulance service.

11 SVENSK SAMMANFATTNING (SWEDISH SUMMARY)

Bakgrund

Ambulanspersonal möter dagligen patienter med ospecifika symtom i sin yrkesutövning. Ospecifika symtom kan även beskrivas som nedsatt allmäntillstånd, trötthet, svaghet och sjukdomskänsla. Ofta hittas inte avvikande vitala parametrar. Sedan tidigare är det känt att var tredje patient med ospecifika symtom på akutmottagningen har ett akut underliggande tillstånd. Därtill är denna grupp patienter övervägande äldre. I ambulanssjukvårdens kontext har denna patientgrupp inte blivit utforskad och det saknas kunskap om ospecifika symtom, såväl som identifieringen av de allvarliga sjukdomstillstånd som en del av dessa patienter har.

Syfte

Det övergripande syftet var att för patienter med ospecifika symtom i ambulansen; beskriva populationen, både dem som transporteras till en akutmottagning och dem som kvarstannar i hemmet, att undersöka om biomarkörer kan bidra till identifieringen av dem som utvecklar allvarlig sjukdom och att beskriva ambulanssjuksköterskors erfarenheter och upplevelser av att vårda dessa patienter.

Metod

Fyra delstudier genomfördes, **studie I** var en retrospektiv, populationsbaserad observationsstudie med syftet att beskriva populationen med ospecifika symtom i ambulansen och förekomsten av allvarlig sjukdom och dödligheten hos de patienter som transporterades till en akutmottagning. Patienter identifierades via ambulansjournalsystemet (CAK-net, Region Stockholm). Vidare inhämtades registerdata för dessa patienter från Patientregistret och Dödsorsaksregistret på Socialstyrelsen. Data analyserades deskriptivt och regressionsanalyser gjordes för att beräkna samband mellan olika patientkaraktäristika och de observerade utfallen. **Studie II** var en retrospektiv, populationsbaserad observationsstudie med syftet att beskriva populationen med ospecifika symtom i ambulansen och förekomsten av allvarlig sjukdom och dödligheten hos de patienter som kvarstannade i hemmet efter bedömning eller hos dem som transporterades till en akutmottagning. Patienter identifierades via ambulansjournalsystemet (CAK-net, Region Stockholm). Vidare inhämtades registerdata för dessa patienter från Patientregistret och Dödsorsaksregistret på Socialstyrelsen. Data analyserades deskriptivt och

regressionsanalyser gjordes för att beräkna samband mellan olika patientkaraktäristika och de observerade utfallen. Därtill jämfördes gruppen med den grupp patienter som transporterades till en akutmottagning. **Studie III** var en intervjustudie med syftet att beskriva ambulanssjuksköterskors upplevelser och erfarenheter av att vårda patienter med ospecifika symtom i ambulansen. Intervjustudien analyserades med kvalitativ innehållsanalys med induktiv ansats enligt Elo och Kyngäs. **Studie IV** var en prospektiv, dubbelblindad, multicenterobservationsstudie med syfte att utröna om biomarkörerna suPAR och laktat kunde användas för att identifiera förekomst av allvarlig sjukdom hos patienter med ospecifika symtom i ambulansen samt dödlighet. Deltagande centra var ambulanssjukvården i Region Stockholm och två regioner i Helsingfors i Finland. Patienter inkluderades av ambulanspersonal efter att de bedömts ha ospecifika symtom samt fallit inom ramen för inklusionskriterierna, samt gett sitt medgivande att delta. Två blodprover togs och patienten transporterades till en akutmottagning. I övrigt fick patienten sedvanlig sjukvård. Patient, ambulanspersonal och sjukhuspersonal var blindade, vilket innebar att blodprovsanalyserna inte var för dem kända. Patientdata inhämtades från det elektroniska ambulansjournalsystemet i respektive region och från elektroniska journalsystem på sjukhusen. Data analyserades deskriptivt och med regressionsanalyser för att undersöka samband mellan patientkaraktäristika och utfall. Sannolikhetsanalyser utfördes för diagnostiska test.

Resultat

Resultaten visar i **Studie I** att patienter med ospecifika symptom i ambulansen som transporteras till en akutmottagning (N=3780) har en allvarlig sjukdom i upp till 35,3% av fallen. Patienterna var äldre med en medianålder på 77 år. Inläggning i slutenvård var 67,7% och vårdtiden var 5 dagar i median. Patienter med allvarlig sjukdom hade högre triagenivåer jämfört med dem utan allvarlig sjukdom. Dödligheten inom 30 dagar var 20,2% (OR 3.1, CI 95%, 2.3–4.0) för dem med allvarlig sjukdom, jämfört med 4,2% i gruppen utan allvarlig sjukdom. Majoriteten av patienterna hade en låg triagenivå enligt RETTS (60,7%) respektive NEWS (76,3%) och bland dem hade 23,9% respektive 28,3% allvarlig sjukdom. Dödigheten inom 30 dagar i gruppen var 13,0% respektive 14,1% för dem med allvarlig sjukdom. I **Studie II**, inkluderades 4744 patienter. Medianåldern var 76 år. Allvarlig sjukdom var prevalent i 29,5% av patienterna. Av totalpopulation kvarstannade 20,3% i hemmet efter ambulanspersonalens bedömning. Bland de som kvarstannade i hemmet hade 6,6% en allvarlig sjukdom, jämfört med 35,3% bland dem som transporterades till en akutmottagning. Dödligheten inom 30 dagar var 17,2% för de patienter som hade allvarlig sjukdom och som

kvarstannade i hemmet jämfört med 20,2% för motsvarande patienter som transporterades till en akutmottagning. I **Studie III** visade ambulanssjuksköterskors erfarenheter och upplevelser att en fördjupad systematisk bedömning upplevs minska lidande och öka patientsäkerheten. Detta genom att åskådliggöra patientens oförklarliga lidande, som är en del i den komplexa bedömningen där patientens lidande inte är tydlig och där närstående spelar en viktig roll i informationsflödet. Ett systematiskt tillvägagångssätt och att erfarenhet kan stärka medicinsk säkerhet är faktorer som kan hjälpa mot de känslor av otillräcklighet som kan uppstå i en vårdsituation. Brist på differentierade vårdnivåer upplevdes som utmanande och främjade inte patientsäkerheten samtidigt som bristen på återkoppling på given vård och patientens utfall ansågs hämmande på ambulanssjuksköterskornas kunskapsutveckling. I **Studie IV** inkluderades 414 patienter. Medianåldern var 82 år och en allvarlig sjukdom var prevalent i 15,2% av patienterna. Dödligheten inom 30 dagar var 9,5% för de patienterna med allvarlig sjukdom, jämfört med 3,1% för dem utan allvarlig sjukdom. AUROC analysen för suPAR och allvarlig sjukdom var 0,63 (95% CI 0.56–0.70), *p < 0.001* och för suPAR och död inom 30 dagar 0.78 (95% CI 0.65–0.91), *p < 0.001*. Sannolikheten att suPAR över 3ng/ml identifierar allvarlig sjukdom var LR+ (positivt sannolikhetsratio) 1,17 och PPV (positivt prediktivt värde) 17,3%. För död inom 30 dagar var motsvarande värden LR+ 4,59 och PPV 16,1. Laktat var inte signifikant prediktiv för vare sig allvarlig sjukdom eller död inom 30 dagar.

Slutsatser

Denna avhandling erbjuder flera slutsatser, varav flera med en klinisk implikation. Resultaten indikerar att identifiering av allvarlig sjukdom när patienten bedöms ha ospecifika symtom är fortsatt svårt och komplicerat. Patienter med ospecifika symtom som kvarstannar i hemmet efter bedömning av ambulanspersonal skiljer sig inte åt från de som transporteras till en akutmottagning avseende symtom, kön eller ålder. De skiljer sig dock i förekomst av allvarlig sjukdom och dödlighet, som i båda fallen är lägre. Allvarlig sjukdom förekommer hos patienter som erhåller hög såväl som låg triagenivå. Dessa triagemodeller baseras på vitala parametrar och indikerar att användningen av dessa som ensamt beslutsstöd inte är säker. Biomarkörer som testats kan inte identifiera allvarlig sjukdom även om de kan ha visst värde för fortsatt handläggning och riskstratifiering utifrån ett mortalitetsperspektiv. Ambulanssjuksköterskor upplever att denna patientgrupp gagnas av en fördjupad systematisk bedömning som kan minska lidande och öka patientsäkerhet samt att organisatoriska faktorer som återkoppling och differentierade vårdnivåer kunde ha positiva effekter på vården i allmänhet och patienter med ospecifika symtom i synnerhet. Resultaten indikerar att bedömningarna är komplexa och att de

objektiva mätvärden som används inte är tillräckliga för att identifiera allvarlig sjukdom, dock finns indikation på att faktorer som inte undersökts inom ramen för denna avhandling kan vara av betydelse för patienten och dennes fortsatta vård.

12 ACKNOWLEDGEMENTS

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14 APPENDIX 1: LIST OF SERIOUS CONDITIONS

System	Diagnosis	ICD-10
Cardiovascular		
Congestive heart failure	Right ventricular failure	I50.0
	Left ventricular failure	I50.1
	Heart failure, unspecified	I50.9
Acute coronary syndrome	Acute myocardial infarction, unspecified	I21.9
	Unstable angina	I20.0
	Acute transmural myocardial infarction of other sites	I21.2
	Acute transmural myocardial infarction of unspecified site	I21.3
	Acute ischaemic heart disease, unspecified	I24.9
Aneurysm and dissection	Dissection of aorta [any part]	I71.0
	Aneurysm and dissection of carotid artery	I72.0
	Aneurysm and dissection of iliac artery	I72.3
	Aneurysm and dissection of artery of lower extremity	I72.4
	Aneurysm and dissection of other precerebral arteries	I72.5
	neurysm and dissection of vertebral artery	I72.6

	Aneurysm and dissection of other specified arteries	I72.8
	Aneurysm and dissection of unspecified site	I72.9
Embolism	Pulmonary embolism with mention of acute cor pulmonale	I26.0
	Pulmonary embolism without mention of acute cor pulmonale	I26.9
	Embolism and thrombosis of abdominal aorta	I74.0
	Embolism and thrombosis of other and unspecified parts of aorta	I74.1
	Embolism and thrombosis of arteries of upper extremities	I74.2
	Embolism and thrombosis of arteries of lower extremities	I74.3
	Embolism and thrombosis of iliac artery	I74.5
Peri/myocarditis	Acute nonspecific idiopathic pericarditis	I30.0
	Infective pericarditis	I30.1
	Other forms of acute pericarditis	I30.8
	Acute pericarditis, unspecified	I30.9
	Infective myocarditis	I40.0
	Other acute myocarditis	I40.8
	Acute myocarditis, unspecified	I40.9

Pulmonary		
Interstitial pulmonary disease	Acute drug-induced interstitial lung disorders	J70.2
	Chronic obstructive pulmonary disease with acute exacerbation, unspecified	J44.1
	Acute respiratory failure	J96.0
Abdominal		
Acute abdomen	Acute appendicitis with generalized peritonitis	K35.2
	Acute appendicitis with localized peritonitis	K35.3
	Acute peritonitis	K65.0
	Disorders of peritoneum in infectious diseases classified elsewhere	K67*
	Acute parametritis and pelvic cellulitis	N73.0
	Female acute pelvic peritonitis	N73.3
Hernias	Bilateral inguinal hernia, with obstruction, without gangrene	K40.0
	Bilateral inguinal hernia, with gangrene	K40.1
	Unilateral or unspecified inguinal hernia, with obstruction, without gangrene	K40.3
	Unilateral or unspecified inguinal hernia, with gangrene	K40.4

	Bilateral femoral hernia, with obstruction, without gangrene	K41.0
	Bilateral femoral hernia, with gangrene	K41.1
	Unilateral or unspecified femoral hernia, with obstruction, without gangrene	K41.3
	Unilateral or unspecified femoral hernia, with gangrene	K41.4
	Umbilical hernia with obstruction, without gangrene	K42.0
	Umbilical hernia with gangrene	K42.1
	Incisional hernia with obstruction, without gangrene	K43.0
	Incisional hernia with gangrene	K43.1
	Parastomal hernia with obstruction, without gangrene	K43.3
	Parastomal hernia with gangrene	K43.4
	Other and unspecified ventral hernia with obstruction without gangrene	K43.6
	Other and unspecified ventral hernia with gangrene	K43.7
Gastrointestinal haemorrhage	Haematemesis	K92.0
	Melaena	K92.1
	Gastrointestinal haemorrhage, unspecified	K92.2

	Ulcer of oesophagus	K22.1
	Perforation of oesophagus	K22.3
	Gastric ulcer, acute with haemorrhage	K25.0
	Gastric ulcer, acute with perforation	K25.1
	Gastric ulcer, acute with both haemmorage and perforation	K25.2
	Duodenal ulcer, acute with haemorrhage	K26.0
	Duodenal ulcer, acute with perforation	K26.1
	Duodenal ulcer, acute with both haemmorage and perforation	K26.2
	Perforation of intestine (nontraumatic)	K63.1
	Peptic ulcer, site unspecified, acute with haemorrhage	K27.0
	Peptic ulcer, site unspecified, acute with perforation	K27.1
	Peptic ulcer, site unspecified, acute with both haemmorage and perforation	K27.2
	Gastrojejunal ulcer, acute with haemorrhage	K28.0
	Gastrojejunal ulcer, acute with perforation	K28.1
	Gastrojejunal ulcer, acute with both haemmorage and perforation	K28.2
	Acute haemorrhagic gastritis	K29.0

Neurological		
Cerebrovascular – ischemic	Cerebral infarction	I63*
Cerebrovascular – haemmorrhagic	Subarachnoid haemorrhage	I60*
	Intracerebral haemorrhage	I61*
	Other nontraumatic intracranial haemorrhage	I62*
Brain abscess/infection	Amoebic brain abscess	A06.6
	Phaeomycotic brain abscess	B43.1
	Tuberculous meningitis	A17.0
	Plague meningitis	A20.3
	Listerial meningitis and meningoencephalitis	A32.1
	Meningococcal meningitis	A39.0
	Viral meningitis	A87*
	Herpesviral meningitis	B00.3
	Varicella meningitis	B01.0
	Varicella encephalitis	B01.1
	Zoster encephalitis	B02.0
	Zoster meningitis	B02.1
	Measles complicated by encephalitis	B05.0

	Measles complicated by meningitis	B05.1
	Mumps meningitis	B26.1
	Candidal meningitis	B37.5
	Bacterial meningitis	G00*
	Meningitis in bacterial diseases classified elsewhere	G01*
	Meningitis in other infectious and parasitic diseases classified elsewhere	G02*
	Meningitis due to other and unspecified causes	G03*
Epilepsy	Status epilepticus	G41*
Inflammatory neuropathy	Guillain-Barré syndrome	G61.0
Infectious		
Pneumonia (only if admitted to hospital care)	HIV disease resulting in Pneumocystis jirovecii pneumonia	B20.6
	HIV disease resulting in lymphoid interstitial pneumonitis	B22.1
	Cytomegaloviral pneumonitis	B25.0
	Influenza with pneumonia, seasonal influenza virus identified	J10.0
	Influenza with other respiratory manifestations, seasonal influenza virus identified	J10.1

	Influenza with pneumonia, virus not identified	J11.0
	Influenza with other respiratory manifestations, virus not identified	J11.1
	Viral pneumonia	J12*
	Pneumonia due to Streptococcus pneumoniae	J13*
	Pneumonia due to Haemophilus influenzae	J14*
	Bacterial pneumonia	J15*
	Pneumonia due to other infectious organisms	J16*
	Pneumonia in diseases classified elsewhere	J17*
	Pneumonia, organism unspecified	J18*
	Acute bronchitis	J20*
	Hypersensitivity pneumonitis due to organic dust	J67*
	Respiratory conditions due to inhalation of chemicals, gases, fumes and vapours	J68*
	Pneumonitis due to solids and liquids	J69*
	Abscess of lung with pneumonia	J85.1
Urinary tract infection	Urinary tract infection, site not specified	N39.0
Cholecystitis	Acute cholecystitis	K81.0

	Calculus of gallbladder with acute cholecystitis	K80.0
Necrotizing fasciitis	Necrotizing fasciitis	M72.6
Sepsis	Salmonella sepsis	A02.1
	Anthrax sepsis	A22.7
	Listerial sepsis	A32.7
	Candidal sepsis	B37.7
	Acute meningococcaemia	A39.2
	Streptococcal sepsis	A40*
	Other sepsis	A41*
	Actinomycotic sepsis	A42.7
	Toxic shock syndrome	A48.3
Septic arthritis	Pyogenic arthritis	M00*
Endocrine, nutritional and metabolic diseases		
	Hypo-osmolality and hyponatraemia	E87.1
	Hyperkalaemia	E87.5
	Hypokalaemia	E87.6
	Addisonian crisis	E27.2
	Nondiabetic hypoglycaemic coma	E15*

	Other disorders of pancreatic internal secretion	E16*
	Hyperglycaemia, unspecified	R73.9
Nephrology/ urology		
	Retention of urine	R33*
	Acute renal failure	N17*
Poisoning/ intoxication (only if admitted to hospital care)		
	Botulism	A05.1
	Accidental poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics	X40*
	Accidental poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified	X41*
	Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified	X42*
	Accidental poisoning by and exposure to other drugs acting on the autonomic nervous system	X43*
	Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances	X44*
	Accidental poisoning by and exposure to alcohol	X45*

	Accidental poisoning by and exposure to organic solvents and halogenated hydrocarbons and their vapours	X46*
Neoplasms		
	All new, acute complications, all deaths within 30 days	C01-C26* C31-C34* C37-C41* C43-C58* C60-C86* C90-C97*
	Neoplasm in situ	D00-D09*