Determining the Diagnostic Accuracy of Various Clinical and Biochemical Parameters in Predicting Specific Severe Infections in Older Adults

Vaesen Dries, KULeuven

Promotor: Van den Bruel Ann, KULeuven

Co-promotor: Struyf Thomas, UAntwerpen

Master of Family Medicine

Masterproef Huisartsgeneeskunde
Academiejaar: 2025 – 2026

©Copyright by KU Leuven

Deze masterproef is een examendocument dat niet werd gecorrigeerd voor eventueel vastgestelde fouten. Met uitzondering van het door de wet toegestaan gebruik, is zonder voorafgaande schriftelijke toestemming van de auteur(s) het overnemen, kopiëren, gebruiken of realiseren van deze uitgave of gedeelten ervan verboden. Voor aanvragen tot of informatie in verband met het overnemen en/of gebruik van gedeelten uit deze publicatie, wendt u zich tot de KU Leuven, Faculteit Geneeskunde, Campus Gasthuisberg O&N2, Herestraat 49 – bus 400, 3000 Leuven.

Voorafgaande schriftelijke toestemming van de promotor(en) is eveneens vereist voor het aanwenden van de in dit afstudeerwerk beschreven (originele) methoden, producten en programma's voor commercieel nut en voor de inzending van deze publicatie ter deelname aan wetenschappelijke prijzen of wedstrijden.

Abstract

Introduction: Serious infections pose a serious threat to older adults due to an increased prevalence of comorbidities and factors such as immunosenescence and frailty. Furthermore, older adults may exhibit more atypical symptoms, which complicates the process of making an accurate diagnosis. Currently, predictive tools that are useful for differentiating between infections in older adults are limited. This study aims to identify clinical signs and biochemical markers that can be used to distinguish between common and serious infections in older adults.

Methods: A retrospective analysis was performed using data from the ROSIE study, a prospective cross-sectional study conducted between April 2021 and July 2023. The study included 494 adults aged 65 or older, who presented to emergency departments and general practices with suspected infectious diseases. Clinical parameters, vital signs, and biomarkers (CRP, procalcitonin, and white blood cell count) were collected. Diagnostic performance was evaluated based on sensitivity, specificity, predictive values, and likelihood ratios for the following predefined infections: pneumonia, acute exacerbation of COPD (AECOPD), acute pyelonephritis, acute cholecystitis, bacteremia, and sepsis.

Results: Pneumonia was the most common infection in both the emergency department and general practice. No single clinical or biochemical marker demonstrated both high sensitivity and specificity. CRP had relatively high sensitivity across all assessed diseases, but its specificity was limited. Clinical symptoms such as lung crepitations in pneumonia and percussion pain of the kidney in pyelonephritis may be useful in confirming those specific diseases, although likelihood ratios were generally moderate. Many parameters showed high negative predictive values, which can be explained by the relatively low prevalence of most assessed diseases.

Conclusion: The utility of individual parameters in distinguishing serious infections in older adults remains limited. Certain symptoms and biomarkers may be more valuable in ruling out specific diseases. The development of predictive models that integrate multiple clinical signs and symptoms for specific diseases may be the next step in helping clinicians distinguish between different serious infections in older adults.

Abstract

Inleiding: Zware infecties vormen een ernstige bedreiging voor ouderen vanwege een verhoogde prevalentie van comorbiditeiten en factoren zoals *immunosenescence* en *frailty*. Bovendien kunnen oudere volwassenen vaker atypische symptomen vertonen, wat het stellen van een juiste diagnose bemoeilijkt. Momenteel zijn er slechts een beperkt aantal predictieve instrumenten beschikbaar die nuttig zijn voor het onderscheiden van infecties bij ouderen. Deze studie tracht klinische symptomen en biochemische markers te identificeren die kunnen worden gebruikt om onderscheid te maken tussen veelvoorkomende en ernstige infecties.

Methoden: Er werd een retrospectieve analyse uitgevoerd op basis van gegevens uit de ROSIE-studie, een prospectief cross-sectioneel onderzoek dat tussen april 2021 en juli 2023 werd uitgevoerd. Het onderzoek omvatte 494 patiënten van 65 jaar en ouder die zich aanmeldden bij spoeddiensten en huisartsenpraktijken met een vermoeden van een infectieuze ziekte. Klinische parameters, vitale functies en biomarkers (CRP, procalcitonine en het aantal leukocyten) werden verzameld. De diagnostische accuraatheden werden geëvalueerd op basis van sensitiviteit, specificiteit, predictieve waarden en likelihood ratio's voor de volgende vooraf gedefinieerde infecties: pneumonie, acute exacerbatie van COPD (AECOPD), acute pyelonefritis, acute cholecystitis, bacteriëmie, en sepsis.

Resultaten: Zowel op de spoedeisende hulp als in de huisartsenpraktijk was pneumonie de meest voorkomende infectie. Geen enkele klinische of biochemische marker vertoonde zowel een hoge sensitiviteit als een hoge specificiteit. CRP had een relatief hoge sensitiviteit voor alle onderzochte aandoeningen, maar de specificiteit ervan was beperkt. Klinische symptomen zoals crepitaties bij auscultatie van de longen bij pneumonie en percussiepijn van de nier bij pyelonefritis, kunnen enig nut hebben bij het bevestigen van die specifieke aandoeningen, hoewel de likelihood ratio's over het algemeen matig waren. Veel parameters vertoonden hoge negatief predictieve waarden, wat kan worden verklaard door de relatief lage prevalentie van de meeste onderzochte aandoeningen.

Conclusie: Het nut van individuele parameters bij het onderscheiden van ernstige infecties bij ouderen blijft beperkt. Bepaalde symptomen en biomarkers kunnen waardevol zijn bij het uitsluiten van specifieke aandoeningen. De ontwikkeling van voorspellende modellen die meerdere klinische tekenen en symptomen voor specifieke aandoeningen integreren, kan de volgende stap zijn om clinici te helpen onderscheid te maken tussen verschillende ernstige infecties bij ouderen.

Table of Contents

Introduction....6
Methods....8
Study design, Setting and Selection of Participants....8
Measurements....8
Statistical Analysis....8
Results....9
Table 1....9
Pneumonia....9
Table 2....9
Table 3....10
Acute COPD Exacerbation....11
Table 4....11
Table 5....12
Pyelonephritis....13
Table 6....13
Table 7....14
Cholecystitis....15
Table 8....15
Table 9....16
Sepsis and Bacteremia....16
Table 10....17
Table 11....17
Discussion....19
References....21

Introduction

Infectious diseases represent a major health risk for older adults (1). In Belgium, COVID-19 was the third leading cause of death in 2020 and 2021 (2). Studies show a rise of the incidence of infections such as pneumonia and urinary tract infections over recent decades (3). Older individuals (65 years of age or older) have an estimated annual risk of 8% of developing a potentially serious infection (3). These infections may result in significant morbidity, including long-term cognitive and functional decline, particularly after conditions such as sepsis (4,5).

The severity of infectious diseases in older adults varies widely. While some individuals experience mild illness, other patients with multiple comorbidities such as chronic obstructive pulmonary disease (COPD) or diabetes, are at higher risk of complications. Struyf et al.[6] defined serious infections in this population as infections associated with a high risk of complications, functional decline, or mortality, requiring timely diagnosis and treatment (6).

Several age-related factors make older adults more susceptible to complications of serious infections. The presence of multiple chronic conditions and factors such as immunosenescence play an important role (7). Immunosenescence refers to the gradual deterioration of the immune system with age (8,9). Inflammaging, a chronic low-grade inflammatory state characterized by elevated levels of pro-inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) further increases the vulnerability of older adults (10). Frailty, defined as a reduction in physiological reserves and increased susceptibility to stressors, is closely related to both immunosenescence and inflammaging (11).

Age-related physiological changes also decrease natural host defenses. For example, reduced cough reflex and impaired mucociliary clearance increase susceptibility to respiratory infections (12,13). Furthermore, older patients frequently present with atypical symptoms. Older adults with pneumonia may not present with fever, cough or chest pain. Instead, they may exhibit nonspecific symptoms such as confusion, general malaise, or falls (14,15,16). This atypical presentation in combination with overlapping symptoms further complicates diagnosis of specific diseases, especially in primary care.

Current predictive tools for identifying serious infections in older adults remain limited. The ROSIE (Recognition of Serious Infections in the Elderly) study developed a general prediction rule based on parameters such as systolic blood pressure, oxygen saturation, and CRP levels (17). However, this tool does not differentiate between specific types of infections. This highlights a significant gap: the need for models that not only identify serious infections but also are able to differentiate between serious infections in older adults.

This study aims to identify clinical symptoms and biochemical markers associated with specific serious infections in older adults. We hypothesize that certain findings may be more indicative of particular infections (e.g., coughing in pneumonia versus pyelonephritis). To address this, we describe the pathophysiological mechanisms underlying common serious infections and their associated clinical signs and laboratory markers.

Fever is a hallmark of infection but may be absent in up to 30% of serious infections in older adults due to impaired cytokine responses (18,19,20,21). Biomarkers such as CRP, white blood cell count (WBC), and procalcitonin (PCT) are widely used in the diagnostic process. CRP is an acute-phase protein produced by the liver in response to inflammation, while PCT levels rise more rapidly and may correlate with bacterial infection severity (22,23,24,25,26,27,28). WBC levels increase as part of the immune response, particularly due to neutrophil activation and recruitment. In older adults, these mechanisms may be impaired to a certain extent, partly due to immunosenescence and chronic inflammation (29,30,31).

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, illustrates the complexity of systemic infection. It involves an exaggerated inflammatory response accompanied by endothelial dysfunction, coagulopathy, and impaired organ perfusion

(32,33,34). These pathophysiologic mechanisms induce multiple clinical features including hypotension partly due to increased nitric oxide production, tachypnoea explained by increased alveolar permeability resulting in pulmonary edema, and changes in mental status, exacerbated by hypoperfusion and influx of neurotoxic molecules into the brain (due to a damaged endothelial barrier) (35,36,37). A hypothesis is that atypical symptoms such as falling may also result from hypoperfusion to the brain in older patients. Biomarkers such as CRP and PCT are often increased during sepsis, as the cytokine storm causes an increase of upregulation of both biomarkers (38). WBC count initially also increases, but may also decrease due to consumption by neutrophil extracellular traps (NET) (39). Bacteremia is defined as the presence of viable bacteria in the blood stream. In bacteremia, there is no dysregulated host response causing organ dysfunction thus separating it from sepsis (40,41,42).

Other infections also exhibit distinct pathophysiological and clinical features. Pneumonia results from infection of the lung parenchyma. Alveolar macrophages activate the inflammatory pathway through phagocytosis of the pathogen. This causes symptoms such as cough, dyspnoea, and sputum production, although atypical presentations are frequent in older patients (43,44,45,46,47,48). Acute exacerbations of COPD are often triggered by a similar pathophysiologic pathway as infectious agents cause the influx of inflammatory molecules into the airways, causing a worsening of symptoms such as dyspnoea and coughing (49). Pyelonephritis, typically caused by ascending urinary tract infections, presents with urinary symptoms, flank pain due to swelling of renal parenchyma and systemic signs of infection, as uro-epithelial cells secrete pro-inflammatory cytokines and activate the inflammatory pathway (50,51,52,53). Cholecystitis is in most cases caused by gallstones blocking the bile duct. Pressure in the gallbladder rises, causing ischemia and inflammation locally. Bacterial colonization furthermore increases local inflammation (54). Abdominal pain can be explained by the swelling of the gallbladder, while systemic symptoms, such as fever, are caused by the systemic release of pro-inflammatory molecules often in a later stage (55).

In summary, older adults are particularly vulnerable to serious infections due to a combination of immunological, physiological, and clinical factors. The heterogeneity in presentation and the limitations of current diagnostic tools underline the need for improved predictive models. This study seeks to identify clinical and biochemical markers that can help in distinguishing between specific serious infections in older patients, thereby supporting earlier diagnosis and more targeted management in primary care and emergency settings.

Methods

This is a quantitative research paper, conducting a retrospective analysis of data collected in the ROSIE study (a prospective cross-sectional study). The goal of the original ROSIE study was to formulate a prediction rule, based on certain clinical signs and biomarkers, that could identify a serious infection in an older adult presenting to the emergency department with an acute infectious disease.

The primary objective of the current study was to identify which clinical and biochemical parameters are most suitable for differentiating between serious infections in older adults presenting to an emergency department (ED) or a general practice (GP). Specifically, the study aimed to determine which biomarkers and clinical findings best discriminate among the following predefined infectious diseases: pneumonia, AECOPD, acute pyelonephritis, acute cholecystitis, bacteremia, and sepsis. A more in-depth explanation and formulation of the approved protocol and setting of the study can be found in the ROSIE study (17).

Study design, Setting and Selection of Participants

The ROSIE study ran from April 2021 to July 2023. There were three participating emergency departments: (a) University Hospitals Leuven, Campus Gasthuisberg (a tertiary academic center, 1949 beds, 72,097 ED visits in 2022, 18 months of recruitment), (b) AZ Voorkempen Malle (a 250-bed regional hospital, 25,704 ED visits in 2022, 26 months of recruitment), and (c) Heilig Hart Hospital Leuven (a 287-bed regional hospital, 21,295 ED visits in 2022, 1.5 months of recruitment). Data from seven participating general practices located in Limburg, Antwerpen and Vlaams-Brabant were also included. Participants were acutely ill adults aged 65 years or older presenting to primary care (either ED or GP) with a clinical suspicion of infection that lasted 10 or more days.

Patients were excluded if they were (a) clinically too unstable for study procedures, (b) immunocompromised, (c) had an indwelling catheter, (d) were recently hospitalized, (e) had surgery, or (f) had already been enrolled in the study. Informed consent was obtained from patients or their legal representatives when required. In the final ROSIE study, only patients that presented to the emergency departments were included. This paper will also include patients that presented to a general practitioner.

Measurements

At presentation in the general practice or emergency department, demographic characteristics, clinical information (vital signs, symptoms suggestive of a (specific) infection, comorbidities such as smoking…), and biochemical parameters (CRP, PCT and WBC count) were recorded by the study nurse or general practitioner. Laboratory data were extracted from electronic health records.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics (version 29.2) and the MedCalc Diagnostic Test Evaluation Calculator (MedCalc Software Ltd, Ostend, Belgium).

Categorical variables were summarized as quantities and percentages. For the retrospective analyses presented in this paper, the diagnostic accuracy of each evaluated parameter was assessed by calculating its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios (LR+ and LR–) for each of the assessed infections. These measures were computed along with their 95% confidence intervals to evaluate the ability of each clinical and biochemical variable to accurately distinguish between the different serious infections.

Results

The prevalence of various infectious diseases differed significantly between general practices and emergency departments (Table 1). Pneumonia was the most common serious infection overall, with a prevalence of 19.6%. This high prevalence was driven by cases in the ED (22%), whereas its prevalence in general practices was considerably lower (4.5%). Nonetheless, pneumonia was also the most common serious infection in general practice together with an acute exacerbation of COPD. AECOPD showed a more balanced prevalence between the two settings (4.5% in general practice; 3.3% in the ED). Acute pyelonephritis, acute cholecystitis, bacteremia and sepsis were not observed in general practice but were present in the ED. The category Other diagnosis accounted for the majority of cases in both settings, although it was particularly high in general practices (91%).

Table 1

Prevalence of the Assessed Diseases in General Practice and the Emergency Department, Expressed as the Number of Observations and the Percentage Relative to the Total Sample Size

Disease	Prevalence *n* (%)	General practice *n* (%)	Emergency department *n* (%)
Pneumonia	97 (19.6)	3 (4.5)	94 (22)
AECOPD	17 (3.4)	3 (4.5)	14 (3.3)
Acute pyelonephritis	13 (2.6)	0 (0)	13 (3)
Acute Cholecystitis	18 (3.6)	0 (0)	18 (4.2)
Bacteremia and sepsis	24 (4.9)	0 (0)	24 (5.6)
Other diagnosis	325 (65.8)	60 (91)	265 (62)

Pneumonia

The results for pneumonia are displayed in Table 2 and Table 3. There were no clinical signs or symptoms with a sensitivity higher than 90%. The clinical symptom with the highest sensitivity was general malaise (83.5%, 95%CI 74.6-90.2), followed by coughing (82.5%, 95% CI 73.4-89.5). There were three clinical findings with a specificity over 90%: fever (temperature higher than 38°C), a systolic blood pressure lower than 100 mmHg and an increased state of confusion (CAM-S score higher than 2). The only parameters with a negative predictive value lower than 80%, were smoking and falls. Dyspnoea, cough and lung crepitations had a NPV above 90%. Lung crepitations had the highest LR+ (3.1, 95% CI 2.5-3.9).

A CRP level higher than 10 mg/l had a sensitivity of 95.9% (95%CI 89.8-98.9), making it the test with the highest sensitivity. No biomarkers had a specificity over 90%, nor were there any clinical findings or biomarkers with a positive predictive value (PPV) higher than 50%. A CRP level higher than 10 mg/l had a NPV above 90%. There were no parameters with a positive likelihood ratio (LR+) higher than 5 and no signs or biomarkers with a negative LR (LR-) lower than 0.2.

Table 2

Missing Data, Sensitivity and Specificity for Clinical Symptoms and Biomarkers in Pneumonia

Clinical Symptom or Biomarker	Missing data *n* (%)	Sensitivity % (95% CI)	Specificity % (95% CI)
Cough	0 (0)	82.5 (73.4-89.5)	58.2 (53.2-63.1)
Sputa	0 (0)	56.7 (46.2-66.7)	70.3 (65.5-74.7)

Dyspnoea	0 (0)	73.2 (63.2-81.7)	64.7 (59.8-69.4)
Lung crepitations	0 (0)	67 (56.7-76.2)	78.3 (74-82.3)
Smoking	196 (40)	6.1 (1.7-14.8)	81.5 (75.9-86.2)
Malaise	0 (0)	83.5 (74.6-90.3)	23.2 (19.1-27.6)
Feeling feverish	1 (0)	54.6 (44.2-64.8)	52.5 (47.5-57.5)
Falls	0 (0)	12.4 (6.6-20.6)	85.1 (81.2-88.5)
T > 38°C	0 (0)	17.5 (10.6-26.6)	91.4 (88.2-94)
HR > 100/min	0 (0)	19.6 (12.2-28.9)	86.7 (82.9-89.8)
RR ≥ 22/min	0 (0)	38.1 (28.5-48.6)	81.9 (77.7-85.5)
Systolic BP < 100 mmHg	0 (0)	6.2 (2.3-13.0)	93 (90.0-95.3)
SpO2≤94%	0 (0)	47.4 (37.2-57.8)	76.8 (72.4-80.9)
CAM-S > 2	0 (0)	3.1 (0.6-8.8)	97.2 (95.1-98.6)
CRP > 10 mg/L	0 (0)	95.9 (89.8-98.9)	25.9 (21.7-30.6)
PCT > 0.2ng/mL	0 (0)	48.5 (38.2-58.8)	70.3 (65.5-74.7)
Abnormal WBC	9 (1.9)	39.2 (29.4-49.6)	71.4 (66.6-75.8)

Table 3

Missing Data, Predictive Values and Likelihood Ratios for Clinical Symptoms and Biomarkers in Pneumonia

Clinical Symptom or Biomarker	**Missing data *n* (%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**Positive LR (95% CI)**	**Negative LR (95% CI)**
Cough	0 (0)	32.5 (29.4-35.9)	93.2 (89.8-95.5)	2 (1.7-2.3)	0.3 (0.2-0.5)
Sputa	0 (0)	31.8 (27-37)	86.9 (84-89.4)	1.9 (1.5-2.4)	0.6 (0.5-0.8)
Dyspnoea	0 (0)	33.6 (29.8-37.8)	90.8 (87.6-93.3)	2.1 (1.7-2.5)	0.4 (0.3-0.6)
Lung crepitations	0 (0)	43 (37.4-46.8)	90.7 (87.9-92.8)	3.1 (2.5-3.9)	0.4 (0.3-0.6)
Smoking	196 (40)	8.5 (3.4-20)	75.3 (73.7-76.9)	0.3 (0.1-0.9)	1.1 (1.1-1.3)

Malaise	0 (0)	21 (19.3-22.8)	85.2 (78-90.3)	1.1 (1-1.2)	0.7 (0.4-1.1)
Feeling feverish	1 (0)	22 (18.6-25.8)	82.6 (78.8-85.7)	1.1 (0.9-1.4)	0.9 (0.7-1.1)
Falls	0 (0)	16.9 (10.2-26.6)	79.9 (78.5-81.2)	0.8 (0.5-1.5)	1 (0.9-1.1)
T > 38°C	0 (0)	33.3 (22.6-46.1)	81.9 (80.5-83.3)	2 (1.2-3.5)	0.9 (0.8-1)
HR > 100/min	0 (0)	26.4 (18.2-36.6)	81.5 (79.9-83)	1.5 (0.9-2.4)	0.9 (0.8-1)
RR ≥ 22/min	0 (0)	33.9 (27-41.6)	84.4 (82.2-86.4)	2.1 (1.5-2.9)	0.8 (0.6-0.9)
Systolic BP < 100 mmHg	0 (0)	17.6 (8.4-33.5)	80.2 (79.3-81.1)	0.9 (0.4-2.1)	1 (0.9-1.1)
SpO2 ≤ 94%	0 (0)	33.3 (27.5-39.7)	85.7 (83.1-87.9)	2 (1.6-2.7)	0.7 (0.6-0.8)
CAM-S > 2	0 (0)	21.4 (7.2-49)	80.4 (79.8-81)	1.1 (0.3-3.9)	1 (1-1)
CRP > 10 mg/L	0 (0)	24.0 (22.8-25.4)	96.3 (90.7-98.5)	1.3 (1.2-1.4)	0.2 (0.1-0.4)
PCT > 0.2ng/mL	0 (0)	28.5 (23.6-34)	84.8 (82-87.2)	1.6 (1.3-2.1)	0.7 (0.6-0.9)
Abnormal WBC	9 (1.9)	25.5 (20.3-31.5)	82.4 (79.8-84.8)	1.4 (1-1.8)	0.8 (0.7-1)

Acute COPD Exacerbation

Results for AECOPD are displayed in Table 4 and Table 5. There were no clinical signs or symptoms with a sensitivity higher than 90%. Coughing was the clinical symptom with the highest sensitivity (88.2%, 95% CI 63.6-98.5), followed by dyspnoea (82.4%, 95% CI 56.6-96.2) and malaise (82.3%, 95% CI 56.6-96.2). An increased state of confusion and a systolic blood pressure lower than 100 mmHg were the 2 parameters with a specificity over 90%. Falls, fever and tachycardia (heart rate > 100/min) had a specificity between 80% and 90%. Smoking had the highest positive LR at 3.3 (95% CI 1.8 to 6.1). Coughing had the lowest negative LR at 0.2 (95% CI 0.1 to 0.8).
A CRP level higher than 10mg/l was the only biomarker with a sensitivity higher than 90% (94.4%, 95% CI 72.7-99.9). All parameters had a PPV lower than 15%. All parameters had a NPV higher than 95%. There were no parameters with a positive LR higher than 5, nor were there any parameters with a negative LR lower than 0.2.

Table 4

Missing Data, Sensitivity and Specificity for Clinical Symptoms and Biomarkers in Acute COPD Exacerbation

Clinical Symptom or Biomarker	**Missing data *n* (%)**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**
Cough	0 (0)	88.2 (63.6-98.5)	51.6 (47-56.1)
Sputa	0 (0)	76.5 (50.1-93.2)	66.5 (62-70.7)
Dyspnoea	0 (0)	82.3 (56.6-96.2)	58.7 (54.1-63.2)
Lung crepitations	0 (0)	41.2 (18.4-67.1)	69.8 (65.5-73.9)

Smoking	196 (40)	46.7 (21.3-73.4)	85.9 (81.2-89.7)
Malaise	0 (0)	82.3 (56.6-96.2)	22 (18.4-26)
Feeling feverish	1 (0)	47.1 (23-72.2)	51 (46.5-55.6)
Falls	0 (0)	17.6 (3.8-43.4)	85.7 (82.3-88.8)
T > 38°C	0 (0)	5.9 (0.1-28.7)	89.5 (86.4-92.1)
HR > 100/min	0 (0)	11.8 (1.5-36.4)	85.3 (81.8-88.4)
RR ≥ 22/min	0 (0)	41.2 (18.4-67.1)	78.6 (74.7-82.2)
Systolic BP < 100 mmHg	0 (0)	5.9 (0.1-28.7)	93.1 (90.4-95.2)
SpO2 ≤ 94%	0 (0)	76.5 (50.1-93.2)	73.8 (69.6-77.7)
CAM-S > 2	0 (0)	5.9 (0.1-28.7)	97.3 (95.4-98.5)
BMI > 25	0 (0)	64.7 (38.3-85.8)	55.6 (51-60.1)
CRP > 10mg/L	0 (0)	94.4 (72.7-99.9)	22.4 (18.8-26.4)
PCT > 0.2 ng/mL	0 (0)	17.6 (3.8-43.4)	66 (61.6-70.3)
Abnormal WBC	9 (1.9)	29.4 (10.3-56)	69.2 (64.8-73.4)

Table 5

Missing Data, Predictive Values and Likelihood Ratios for Clinical Symptoms and Acute COPD Exacerbation

Clinical Symptom or Biomarker	**Missing data *n* (%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**Positive LR (95% CI)**	**Negative LR (95% CI)**
Cough	0 (0)	6.1 (5.1- 7.3)	99.2 (97.1-99.8)	1.8 (1.5-2.2)	0.2 (0.1-0.8)
Sputa	0 (0)	7.5 (5.7-9.8)	98.8 (97.1-99.5)	2.3 (1.7-3)	0.3 (0.1-0.8)
Dyspnoea	0 (0)	6.6 (5.3-8.3)	98.9 (97.1-99.6)	2 (1.6-2.5)	0.3 (0.1-0.8)
Lung crepitations	0 (0)	4.6 (2.6-8)	97.1 (95.7-98)	1.4 (0.8-2.5)	0.8 (0.6-1.3)
Smoking	196 (40)	14.9 (8.7-24.4)	96.8 (95-98)	3.3 (1.8-6.1)	0.6 (0.4-1)
Malaise	0 (0)	3.6 (2.9-4.5)	97.2 (92.5-99)	1.1 (0.8-1.3)	0.8 (0.3-2.3)
Feeling feverish	1 (0)	3.3 (2-5.4)	96.4 (94.5-97.7)	1 (0.6-1.6)	1 (0.7-1.6)
Falls	0 (0)	4.2 (1.5-11.2)	96.7 (95.9-97.3)	1.2 (0.4-3.5)	1 (0.8-1.2)
T > 38°C	0 (0)	2 (0.3-12)	96.4 (95.9-96.8)	0.6 (0.1-3.8)	1.1 (0.9-1.2)
HR > 100/min	0 (0)	2.8	96.5	0.8	1

		(0.8-9.7)	(95.8-97)	(0.2-3)	(0.9-1.2)
RR ≥ 22/min	0 (0)	6.4	97.4	1.9	0.8
		(3.6-11.1)	(96.2-98.2)	(1.1-3.5)	(0.5-1.1)
Systolic BP < 100 mmHg	0 (0)	2.9	96.5	0.8	1
		(0.4-17.3)	(96.1-96.9)	(0.1-5.9)	(0.9-1.1)
SpO2 ≤ 94%	0 (0)	9.4	98.9	2.9	0.3
		(7.1-12.3)	(97.4-99.5)	(2.1-4)	(0.1-0.8)
CAM-S > 2	0 (0)	7.1	96.7	2.2	1
		(1.1-35.7)	(96.3-97)	(0.3-15.6)	(0.9-1.1)
BMI > 25	0 (0)	4.9	97.8	1.5	0.6
		(3.5-7)	(95.8-98.8)	(1-2.1)	(0.3-1.2)
CRP > 10mg/L	0 (0)	4.4	99.1	1.2	0.2
		(3.9-4.9)	(94-99.9)	(1.1-1.4)	(0-1.7)
PCT > 0.2 ng/mL	0 (0)	1.8	95.7	0.5	1.2
		(0.7-5)	(94.7-96.6)	(0.2-1.5)	(1-1.6)
Abnormal WBC	9 (1.9)	3.4	96.4	1	1
		(1.6-6.8)	(95.2-97.4)	(0.5-2)	(0.8-1.4)

Pyelonephritis

Results for pyelonephritis are displayed in Table 6 and Table 7. There were no clinical findings with a sensitivity over 90%. General malaise had the highest sensitivity of the clinical symptoms at 76.9% (95% CI 46.2-95). Pollakiuria, percussion pain of the kidney, fever, systolic blood pressure lower than 100mmHg and an increased state of confusion all had a specificity over 90%. Percussion pain of kidney was the only parameter with a LR+ higher than 5 (5.7, 95% CI 1.4 to 22.7).
CRP had a sensitivity of 92.9% (95% CI 66.1-99.8). There were no clinical findings nor biomarkers with a PPV over 15%. All parameters had a NPV higher than 95%.There were no parameters with a LR- lower than 0.2.

Table 6

Missing Data, Sensitivity and Specificity for Clinical Symptoms and Biomarkers in Pyelonephritis

Clinical Symptom or Biomarker	**Missing data *n* (%)**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**
Dysuria	0 (0)	30.8	89.8
		(9.1-61.4)	(85.6-93)
Pollakiuria	0 (0)	15.4	95.2
		(1.9-45.5)	(92.9-97)
Percussion pain kidney	0 (0)	15.4	97.3
		(1.9-45.5)	(95.4-98.5)
Abdominal pain	0 (0)	53.9	74.6
		(25.1-80.8)	(70.5-78.5)
Abdominal irritation	0 (0)	38.5	85.7
		(13.9-68.4)	(82.2-88.7)
Malaise	0 (0)	76.9	21.8
		(46.2-95)	(18.2-25.8)
Feeling feverish	1 (0)	69.2	51.7
		(38.6-90.9)	(47.1-56.2)
Falls	0 (0)	23.1	85.9
		(5-53.8)	(82.4-88.8)
Gender	0 (0)	53.9	50.3
		(25.1-80.8)	(45.8-54.9)
T > 38°C	0 (0)	38.5	90.4
		(13.9-68.4)	(87.5-92.9)

HR > 100/min	0 (0)	7.7 (0.2-36)	85.2 (81.8-88.3)
RR ≥ 22/min	0 (0)	7.7 (0.2-36)	77.5 (73.5-81.2)
Systolic BP < 100 mmHg	0 (0)	7.7 (0.2-36)	93.1 (90.5-95.2)
SpO2 ≤ 94%	0 (0)	30.8 (9.1-61.4)	72.1 (67.9-76.1)
CAM-S > 2	0 (0)	7.1 (0.2-33.9)	97.1 (95.2-98.4)
CRP > 10mg/L	0 (0)	92.9 (66.1-99.8)	22.2 (18.6-26.2)
PCT > 0.2ng/ml	0 (0)	76.9 (46.2-95)	67.8 (63.4-71.9)
Abnormal WBC	9 (1.9)	50.0 (21.1-78.9)	69.8 (65.4-73.9)

Table 7

Missing Data, Predictive Values and Likelihood Ratios for Clinical Symptoms and Biomarkers in Pyelonephritis

Clinical Symptom or Biomarker	**Missing data *n* (%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**Positive LR (95% CI)**	**Negative LR (95% CI)**
Dysuria	0 (0)	12.1 (5.4-25.1)	96.6 (95.2-97.6)	3 (1.2-7.3)	0.8 (0.5-1.1)
Pollakiuria	0 (0)	8 (2.2-24.9)	97.7 (97.1-98.1)	3.2 (0.8-12.2)	0.9 (0.7-1.1)
Percussion pain kidney	0 (0)	13.3 (3.7-38)	97.7 (97.1-98.2)	5.7 (1.4-22.7)	0.9 (0.7-1.1)
Abdominal pain	0 (0)	5.4 (3.3-8.8)	98.4 (97.1-99.1)	2.1 (1.2-3.6)	0.6 (0.3-1.1)
Abdominal irritation	0 (0)	6.8 (3.4-13)	98.1 (97.1-98.8)	2.7 (1.3-5.5)	0.7 (0.5-1.1)
Malaise	0 (0)	2.6 (1.9-3.5)	97.2 (92.8-99)	1 (0.7-1.3)	1.1 (0.4-2.9)
Feeling feverish	1 (0)	3.7 (2.6-5.3)	98.4 (96.5-99.3)	1.4 (1-2.1)	0.6 (0.3-1.4)
Falls	0 (0)	4.2 (1.6-10.9)	97.6 (96.8-98.2)	1.6 (0.6-4.5)	0.9 (0.7-1.2)
Gender	0 (0)	2.9 (1.4-4.5)	97.6 (95.7-98.7)	1.1 (0.7-1.8)	0.9 (0.5-1.7)
T > 38°C	0 (0)	9.8 (4.9-18.6)	98.2 (97.2-98.8)	4 (1.9-8.4)	0.7 (0.4-1.1)
HR > 100/min	0 (0)	1.4 (0.2-8.6)	97.2 (96.9-97.6)	0.5 (0.1-3.5)	1.1 (0.9-1.3)
RR ≥ 22/min	0 (0)	0.9 (0.1-5.8)	96.9 (96.3-97.3)	0.3 (0.1-2.3)	1.2 (1-1.4)
Systolic BP < 100 mmHg	0 (0)	2.9 (0.5-4.5)	97.4 (97-97.8)	1.1 (0.2-7.6)	1 (0.8-1.2)
SpO2 ≤ 94%	0 (0)	2.9 (1.3-6.4)	97.5 (96.4-98.2)	1.1 (0.5-2.5)	1 (0.7-1.4)
CAM-S > 2	0 (0)	6.7 (1-33.6)	97.3 (96.9-97.7)	2.5 (0.3-17.4)	1 (0.8-1.1)
CRP > 10mg/L	0 (0)	3.4	99.1	1.2	0.3

		(2.9-3.9)	(94.1-99.9)	(1-1.4)	(0.1-2.1)
PCT > 0.2ng/ml	0 (0)	6.1	99.1	2.4	0.3
		(4.5-8.2)	(97.6-99.7)	(1.7-3.3)	(0.1-0.9)
Abnormal WBC	9 (1.9)	4	98.2	1.6	0.7
		(2.3-7)	(96.9-99)	(0.9-3)	(0.4-1.3)

Cholecystitis

Results for cholecystitis are displayed in Table 8 and Table 9. There were no parameters with a sensitivity higher than 90%. Abdominal irritation and a CRP level higher than 10mg/l had the highest sensitivity at 83.3% (95% CI 58.6-96.4). A systolic blood pressure lower than 100 mmHg had a specificity of 93.1% (95% CI 90.4-95.2), an increased state of confusion had a specificity of 97.3% (95% CI 95.4-98.5). There were no parameters with a PPV higher than 25%. All parameters had a NPV over 95%. Abdominal irritation had the only LR+ over 5 (6.7, 95% CI 4.9 to 9.2) while also having a LR- of 0.2 (95% CI 0.1 to 0.5).

Table 8

Missing Data, Sensitivity and Specificity for Clinical Symptoms and Biomarkers in Cholecystitis

Clinical Symptom or Biomarker	**Missing data *n* (%)**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**
Abdominal pain	0 (0)	66.7 (41.0-86.7)	75.4 (71.3-79.2)
Abdominal irritation	0 (0)	83.3 (58.6-96.4)	87.6 (84.3-90.4)
Malaise	0 (0)	72.2 (46.5-90.3)	21.6 (18-25.6)
Feeling feverish	1 (0)	33.3 (13.3-59)	50.5 (45.9-55.1)
Falls	0 (0)	5.3 (0.1-26.0)	85.1 (81.6-88.2)
Gender	0 (0)	72.2 (46.5-90.3)	51.0 (46.5-55.6)
T > 38°C	0 (0)	5.3 (0.1-26.0)	89.3 (86.2-91.9)
HR > 100/min	0 (0)	16.7 (3.6-41.4)	85.5 (82.0-88.5)
RR ≥ 22/min	0 (0)	11.1 (1.4-34.7)	77.5 (73.5-81.2)
Systolic BP < 100 mmHg	0 (0)	5.6 (0.1-27.3)	93.1 (90.4-95.2)
SpO2 ≤ 94%	0 (0)	5.6 (0.1-27.3)	71.2 (66.9-75.2)
CAM-S > 2	0 (0)	5.6 (0.1-27.3)	97.3 (95.4-98.5)
BMI > 30	0 (0)	22.2 (6.4-47.6)	81.5 (77.7-84.9)
CRP > 10 mg/L	0 (0)	83.3 (58.6-96.4)	21.9 (18.2-25.8)
PCT > 0.2ng/ml	0 (0)	50.0 (26.0-74.0)	67.2 (62.8-71.4)
Abnormal WBC	9 (1.9)	33.3 (13.3-59)	69.4 (65-73.5)

Table 9

Missing Data, Predictive Values and Likelihood Ratios for Clinical Symptoms and Biomarkers in Cholecystitis

Clinical Symptom or Biomarker	Missing data *n* (%)	PPV % (95% CI)	NPV % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Abdominal pain	0 (0)	9.3 (6.7-12.8)	98.4 (96.9-99.1)	2.7 (1.9-3.9)	0.4 (0.2-0.8)
Abdominal irritation	0 (0)	20.3 (15.6-25.9)	99.3 (98-99.7)	6.7 (4.9-9.2)	0.2 (0.1-0.5)
Malaise	0 (0)	3.4 (2.5-5.7)	95.4 (90.6-97.8)	0.9 (0.7-1.2)	1.3 (0.6-2.8)
Feeling feverish	1 (0)	2.5 (1.3-4.7)	95.2 (93.5-96.6)	0.7 (0.3-1.3)	1.3 (0.9-1.9)
Falls	0 (0)	1.4 (0.2-8.8)	95.7 (95.3-96.2)	0.3 (0.1-2.4)	1.1 (1-1.2)
Gender	0 (0)	5.3 (4.0-7.0)	98 (95.8-99)	1.5 (1.1-2)	0.5 (0.3-1.1)
T > 38°C	0 (0)	1.9 (0.3-11.8)	95.9 (95.5-96.3)	0.5 (0.1-3.4)	1.1 (0.9-1.2)
HR > 100/min	0 (0)	4.2 (1.5-11.1)	96.5 (95.7-97.1)	1.1 (0.4-3.3)	1 (0.8-1.2)
RR ≥ 22/min	0 (0)	1.8 (0.5-6.5)	95.8 (95.1-96.5)	0.5 (0.1-1.9)	1.1 (1-1.4)
Systolic BP < 100 mmHg	0 (0)	2.9 (0.4-17.3)	96.3 (95.9-96.7)	0.8 (0.1-5.5)	1 (0.9-1.1)
SpO2 ≤ 94%	0 (0)	0.7 (0.1-4.7)	95.2 (94.6-95.8)	0.2 (0-1.3)	1.3 (1.2-1.5)
CAM-S > 2	0 (0)	7.1 (1.1-35.8)	96.5 (96.0-96.8)	2 (0.3-14.7)	1 (0.9-1.1)
BMI > 30	0 (0)	4.3 (1.8-9.9)	96.5 (95.6-97.3)	1.2 (0.5-2.9)	0.9 (0.7-1.2)
CRP > 10 mg/L	0 (0)	3.9 (3.2-4.8)	97.2 (92.4-99)	1.1 (0.9-1.3)	0.8 (0.3-2.2)
PCT > 0.2ng/ml	0 (0)	5.5 (3.5-8.5)	97.3 (95.7-98.3)	1.5 (0.9-2.5)	0.7 (0.5-1.2)
Abnormal WBC	9 (1.9)	4 (2.1-7.6)	96.4 (95.1-97.4)	1.1 (0.6-2.1)	1 (0.7-1.3)

Sepsis and Bacteremia

Results for sepsis and bacteremia are displayed in Table 10 and Table 11. There were no clinical symptoms with a sensitivity over 80%. A CRP level higher than 10 mg/l was the only parameter with a sensitivity over 90% (91.7%, 95% CI 73- 99). Petechiae, fever, a systolic blood pressure lower than 100mmHg, an increased state of confusion and an altered mental status (GCS < 15) all had a specificity of 90% or higher. There were no parameters with a PPV higher than 25%. All parameters had a NPV higher than 90%. A systolic blood pressure lower than 100 mmHg had a LR+ of 5.1 (95% CI 2.5-10.5).

There were no other parameters with a LR+ above 5. There were no parameters with a LR- lower than 0.2.

Table 10

Missing Data, Sensitivity and Specificity for Clinical Symptoms and Biomarkers in Sepsis and Bacteremia

Clinical Symptom or Biomarker	Missing data *n* (%)	Sensitivity % (95% CI)	Specificity % (95% CI)
Dyspnoea	0 (0)	33.3 (15.6-55.3)	56.8 (52.2-61.3)
Petechiae	0 (0)	4.0 (0.1-20.4)	99.2 (97.8-99.8)
Malaise	0 (0)	79.2 (57.9-92.9)	21.9 (18.3-25.9)
Feeling feverish	1 ((0)	58.3 (36.6-77.9)	51.6 (47-56.2)
Falls	0 (0)	20.8 (7.1-42.1)	86 (82.5-89.0)
T > 38°C	0 (0)	16.7 (4.7-37.4)	90.0 (86.9-92.6)
HR > 100/min	0 (0)	20.8 (7.1-42.1)	85.7 (82.2-88.8)
RR ≥ 22/min	0 (0)	20.8 (7.1-42.1)	77.9 (73.8-81.5)
Systolic BP < 100 mmHg	0 (0)	29.2 (12.6-51.1)	94.3 (91.8-96.2)
Diastolic BP < 60 mmHg	0 (0)	54.2 (32.8-74.5)	82.3 (78.6-85.7)
SpO2 ≤ 94%	0 (0)	29.2 (12.6-51.1)	72.1 (67.8-76.1)
CAM-S > 2	0 (0)	8.3 (1-27)	97.5 (95.6-98.7)
GCS < 15	0 (0)	4.2 (0.1-21.1)	93.6 (91.0-95.7)
CRP > 10mg/L	0 (0)	91.7 (73.0-99.0)	22.3 (18.6-26.4)
PCT > 0.2ng/mL	0 (0)	75 (53.3-90.2)	68.7 (64.3-72.9)
Abnormal WBC	9 (1.9)	39.1 (19.7-61.5)	69.7 (65.3-73.9)

Table 11

Missing Data, Predictive Values and Likelihood Ratios for Clinical Symptoms and Biomarkers in Sepsis and Bacteremia

Clinical Symptom or Biomarker	Missing data *n* (%)	PPV % (95% CI)	NPV % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Dyspnoea	0 (0)	3.8 (2.2-6.5)	94.3 (92.6-95.7)	0.8 (0.4-1.4)	1.2 (0.9-1.6)
Petechiae	0 (0)	20.0 (2.8-68.3)	95.1 (94.7-95.5)	4.7 (0.6-40.5)	1 (0.9-1.1)

Malaise	0 (0)	4.9 (4-6)	95.4 (90.3-97.9)	1 (0.8-1.2)	0.9 (0.4-2.1)
Feeling feverish	1 ((0)	5.8 (4.2-8.1)	96.0 (93.7-97.5)	1.2 (0.8-1.7)	0.8 (0.5-1.3)
Falls	0 (0)	7.0 (3.3-14.6)	95.5 (94.5-96.3)	1.5 (0.7-3.3)	0.9 (0.8-1.1)
T > 38°C	0 (0)	7.8 (3.2-17.8)	95.5 (94.6-96.2)	1.7 (0.7-4.2)	0.9 (0.8-1.1)
HR > 100/min	0 (0)	6.9 (3.2-14.4)	95.5 (94.5-96.3)	1.5 (0.7-3.3)	0.9 (0.8-1.1)
RR ≥ 22/min	0 (0)	4.6 (2.1-9.7)	95.1 (94.0-96.0)	0.9 (0.4-2.1)	1 (0.8-1.3)
Systolic BP < 100 mmHg	0 (0)	20.6 (11.2-34.8)	96.3 (95.3-97.1)	5.1 (2.5-10.5)	0.8 (0.6-1)
Diastolic BP < 60 mmHg	0 (0)	13.5 (9.4-19.2)	97.2 (95.8-98.2)	3.1 (2-4.7)	0.6 (0.4-0.9)
SpO2 ≤ 94%	0 (0)	5.1 (2.7-9.2)	95.2 (93.9-96.3)	1.1 (0.6-2)	1 (0.8-1.3)
CAM-S > 2	0 (0)	14.3 (3.8-41.3)	95.4 (94.8-95.9)	3.3 (0.8-13.8)	0.9 (0.8-1.1)
GCS < 15	0 (0)	3.2 (0.5-19)	95.0 (94.6-95.4)	0.7 (0.1-4.6)	1 (0.9-1.1)
CRP > 10mg/L	0 (0)	5.7 (5.0-6.4)	98.1 (93.2-99.5)	1.2 (1-1.3)	0.4 (0.1-1.4)
PCT > 0.2ng/mL	0 (0)	10.9 (8.6-13.8)	98.2 (96.4-99.1)	2.4 (1.8-3.1)	0.4 (0.2-0.7)
Abnormal WBC	9 (1.9)	6.0 (3.6-9.8)	95.8 (94.3-97.0)	1.3 (0.8-2.2)	0.9 (0.6-1.2)

Discussion

The primary aim of this study was to identify clinical signs and biomarkers that help differentiate between specific serious infections in older adults presenting to the emergency department or general practice. Overall, 34% of patients presenting to the emergency department and 9% of patients presenting to general practice were diagnosed with one of the predefined serious infections. Pneumonia was the most prevalent serious infection in both settings.
Across all assessed infections, CRP > 10 mg/L consistently demonstrated the highest sensitivity (ranging from 83% to 96%), making it the most useful parameter for ruling out a serious infection when normal. However, its specificity was low in all conditions, limiting its value for confirming (specific) serious infections.

For pneumonia, cough, dyspnoea, general malaise and lung crepitations were the most sensitive clinical findings (82.5%, 73.2%, 83.5% and 67.0%, respectively), although none had sufficient specificity to confirm the diagnosis independently. Their absence, in combination with a low CRP, may help exclude pneumonia in older adults. Similarly for infectious AECOPD, cough, dyspnoea and general malaise showed the highest sensitivities (88.2%, 82.3% and 82.3% respectively). A normal oxygen saturation, no increased sputum production and the absence of cough and dyspnoea combined with normal CRP levels reduced the likelihood of the diagnosis, but confirmatory value remained limited. In acute pyelonephritis, percussion pain of the kidney showed the highest specificity and the only positive likelihood ratio above 5, suggesting potential confirmatory value when present, although this result is based on small numbers. Increased PCT levels were sensitive but non-specific. Abdominal irritation seemed to be the most useful clinical sign in cholecystitis, with a high sensitivity, a positive likelihood ratio above 5 and a negative likelihood ratio of 0.2. In sepsis and bacteremia, hypotension (systolic blood pressure < 100 mmHg) had the highest positive likelihood ratio. CRP again showed high sensitivity but poor specificity. Overall, no single clinical sign or biomarker was sufficient to confidently confirm a specific infection. Most parameters showed greater utility in ruling out rather than ruling in disease.
A major strength of this study is the relatively large overall sample size and the rather large amount of data that was gathered. The selection of clinical symptoms and biomarkers was partly informed by the systematic review of Struyf et al (54). Also, this study is a post-hoc analysis of prospectively gathered data. However, multiple limitations must be accounted for. First, the number of patients with certain infections (e.g. pyelonephritis, cholecystitis, AECOPD) was very small, resulting in wide confidence intervals and reduced statistical precision. Another important remark to make is the fact that these results were combined from data gathered at different hospitals and general practices. These two different settings have different pre-test probabilities, so generalizing these results for general practice and emergency departments separately may not be accurate. Even more, infections like sepsis and cholecystitis did not present in the general practices in our study. As a result, the diagnostic performance of certain parameters may primarily reflect emergency department populations rather than true first-line primary care presentations. As this was a multicenter study, patients were assessed by multiple different care providers who interpret clinical findings differently (observer bias). Patients gave subjective answers when reporting symptoms, creating possible reporting bias. Next, overlapping symptoms between infections and age-related (atypical) presentations of other (non-infectious) diseases, as explained earlier, likely reduced diagnostic discrimination.

Our findings are in line with previous research demonstrating that older adults frequently present with non-specific or atypical symptoms in serious infections such as pneumonia, limiting the diagnostic value of isolated clinical signs (55,56). The high sensitivity but low specificity of CRP aligns

with earlier studies showing that inflammatory markers are useful for exclusion but insufficient for confirmation when used alone (57,58). In other studies, PCT has been shown to have higher sensitivity/specificity values in detecting sepsis compared to other biomarkers (59,60). A possible reason this was not detected in our study was because of inflammaging and immunosenescence, as explained earlier.

In both emergency and general practice settings, physicians should systematically assess vital signs (blood pressure, respiratory rate, oxygen saturation, temperature), mental status, and perform a focused organ-specific examination in every older patient with suspected infection. CRP could be useful as a rule-out tool when low, but elevated values should always be interpreted in clinical context, accounting for other diseases and inflammaging. Also, the predetermined cut-off values for an elevated CRP-level were rather low, meaning higher cut-off values could potentially differentiate even more between serious infectious pathologies and other diseases. In clinical practice, particular attention should be paid to hypotension (possible sepsis), abdominal irritation (possible cholecystitis), percussion pain of the kidney (possible pyelonephritis), and lung auscultation abnormalities (possible pneumonia). Given the limited confirmatory power of individual findings, clinical reasoning and safety-netting remain essential.

Future research should focus on developing and validating multivariable prediction models combining clinical signs and biomarkers to improve diagnostic discrimination between specific serious infections in older adults presenting to primary care practices. Larger primary care cohorts are particularly needed to better develop predictive tools in differentiating serious infections in older adults presenting to general practitioners. Additionally, studies exploring changes in biomarker values during a period of time rather than single date measurements may further enhance clinical decision-making.

References

1. Eurostat. Causes of death statistics by age group [Internet]. European Commission; 2021 [Cited 2025 Apr 20]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Causes_of_death_statistics_by_age_group#Most_frequent_causes_of_death_in_the_EU_in_2021

2. Statbel. Causes of death [Internet]. Statistics Belgium; 2021 [Cited 2025 Apr 20]. Available from: https://statbel.fgov.be/en/themes/population/mortality-life-expectancy-and-causes-death/causes-death#news

3. Struyf T, Nuyts S, Tournoy J, Vaes B, Verbakel JY, Van den Bruel A. Burden of infections on older patients presenting to general practice: a registry-based study. Fam Pract. 2021 Mar 29;38(2):166-172.

4. Mankowski RT, Anton SD, Ghita GL, Brumback B, Cox MC, Mohr AM, Leeuwenburgh C, Moldawer LL, Efron PA, Brakenridge SC, Moore FA. Older sepsis survivors suffer persistent disability burden and poor long-term survival. J Am Geriatr Soc. 2020 Sep;68(9):1962-1969.

5. Caljouw MA, Kruijdenberg SJ, de Craen AJ, Cools HJ, den Elzen WP, Gussekloo J. Clinically diagnosed infections predict disability in activities of daily living among the oldest-old in the general population: the Leiden 85-plus Study. Age Ageing. 2013 Jul;42(4):482-488.

6. Struyf T, Tournoy J, Verbakel JY, Van den Bruel A. International consensus definition of a serious infection in a geriatric patient presenting to ambulatory care. J Am Med Dir Assoc. 2020 May;21(5):655-659.

7. Cillóniz C, Polverino E, Ewig S, Aliberti S, Gabarrús A, Menéndez R, Mensa J, Blasi F, Torres A. Impact of age and comorbidity on cause and outcome in community-acquired pneumonia. Chest. 2013 Sep;144(3):999-1007.

8. Liu Z, Liang Q, Ren Y, Guo C, Ge X, Wang L, Cheng Q, Luo P, Zhang Y, Han X. Immunosenescence: molecular mechanisms and diseases. Signal Transduct Target Ther. 2023 May 13;8(1):200.

9. Wang Y, Dong C, Han Y, Gu Z, Sun C. Immunosenescence, aging and successful aging. Front Immunol. 2022 Aug 2;13:942796.

10. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018 Sep;15(9):505-522.

11. Proietti M, Cesari M. Frailty: what is it? Adv Exp Med Biol. 2020;1216:1-7

12. Bailey KL. Aging diminishes mucociliary clearance of the lung. Adv Geriatr Med Res. 2022; 4(2): e220005.

13. Won HK, Yoon SJ, Song WJ. The double-sidedness of cough in the elderly. Respir Physiol Neurobiol. 2018 Nov; 257: 65-69.

14. Scott MM, Liang SY. Infections in older adults. Emerg Med Clin North Am. 2021 May;39(2):379-394.

15. Torres A, Cilloniz C, Niederman MS, Menéndez R, Chalmers JD, Wunderink RG, van der Poll T. Pneumonia. Nat Rev Dis Primers. 2021 Apr 8;7(1):25.

16. Fein AM. Pneumonia in the elderly: overview of diagnostic and therapeutic approaches. Clin Infect Dis. 1999 Apr;28(4):726-729.

17. Struyf T, Powaga L, Sabbe M, Léonard N, Myatchin I, Van Calster B, Tournoy J, Buntinx F, Liesenborghs L, Verbakel JY, Van den Bruel A. Recognition of serious infections in the elderly visiting the emergency department: the development of a diagnostic prediction model (ROSIE). Geriatrics (Basel). 2025 Apr 25;10(3):60.

18. Norman DC, Yoshikawa TT. Fever in the elderly. Infect Dis Clin North Am. 1996 Mar;10(1):93-99.

19. Balli S, Shumway KR, shran S. Physiology, fever. In: *Statpearls* [Internet]. Treasure Island (FL): Statpearls Publishing; 2024 [Cited 2025 Apr 28]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562334/

20. Mackowiak PA, Bartlett JG, Borden EC, Goldblum SE, Hasday JD, Munford RS, Nasraway SA, Stolley PD, Woodward TE. Concepts of fever: recent advances and lingering dogma. Clin Infect Dis. 1997 Jul;25(1):119-138.

21. Ayoub SS. Paracetamol (acetaminophen): A familiar drug with an unexplained mechanism of action. Temperature (Austin). 2021 Mar 16;8(4):351-371.

22. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol. 2018 Apr 13;9:754.

23. Anush MM, Ashok VK, Sarma RI, Pillai SK. Role of C-reactive protein as an indicator for determining the outcome of sepsis. Indian J Crit Care Med. 2019 Jan;23(1):11-14.

24. Cleland DA, Eranki AP. Procalcitonin. Updated 2023 Apr 23. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 [Cited 2025 Apr 28]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539794/

25. Maves RC, Enwezor CH. Uses of procalcitonin as a biomarker in critical care medicine. Infect Dis Clin North Am. 2022 Dec;36(4):897-909.

26. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. BMC Med. 2011 Sep 22;9:107.

27. Harikrishna J, Mohan A, Kalyana Chakravarthi DP, Chaudhury A, Kumar BS, Sarma KVS. Serum procalcitonin as a biomarker of bloodstream infection & focal bacterial infection

in febrile patients. Indian J Med Res. 2020 Apr;151(4):342-349.

28. Liu HH, Guo JB, Geng Y, Su L. Procalcitonin: present and future. Ir J Med Sci. 2015 Sep;184(3):597-605.

29. Tigner A, Ibrahim SA, Murray IV. Histology, white blood cell. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [Cited 2025 Apr 28]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563148/

30. Riedel S. Predicting bacterial versus viral infection, or none of the above: Current and future prospects of biomarkers. Clin Lab Med. 2019 Sep;39(3):453-472.

31. Honda T, Uehara T, Matsumoto G, Arai S, Sugano M. Neutrophil left shift and white blood cell count as markers of bacterial infection. Clin Chim Acta. 2016 Jun 1;457:46-53.

32. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The third international consensus definitions for sepsis and septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-810.

33. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol. 2017 Jul;39(5):517-528.

34. Arora J, Mendelson AA, Fox-Robichaud A. Sepsis: network pathophysiology and implications for early diagnosis. Am J Physiol Regul Integr Comp Physiol. 2023 May;324(5):R613-R624.

35. Bullock B, Benham MD. Bacterial sepsis. Updated 2023 May 21. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 [Cited 2025 May 1]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537054/

36. Zampieri FG, Park M, Machado FS, Azevedo LC. Sepsis-associated encephalopathy: not just delirium. Clinics (Sao Paulo). 2011;66(10):1825-1831.

37. Carter BL, Underwood J. Sepsis and the brain: a review for acute and general physicians. Clin Med (Lond). 2022 Sep;22(5):392-395.

38. Faix JD. Biomarkers of sepsis. Crit Rev Clin Lab Sci. 2013 Jan-Feb;50(1):23-36.

39. Makino I, Tajima H, Kitagawa H, Nakagawara H, Miyashita T, Nakanuma S, Hayashi H, Takamura H, Fushida S, Ohta T. A case of severe sepsis presenting marked decrease of neutrophils and interesting findings on dynamic CT. Am J Case Rep. 2015 May;16:322-327.

40. Smith DA, Nehring SM. Bacteremia. Updated 2023 Jul 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 [Cited 2025 May 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441979/

41. Huerta LE, Rice TW. Pathologic difference between sepsis and bloodstream infections. J Appl Lab Med. 2019 Jan;3(4):654-663.

42. Abraham L, Bamberger DM. Staphylococcus aureus bacteremia: contemporary management. Mo Med. 2020 Jul-Aug;117(4):341-345.

43. Lanks CW, Musani AI, Hsia DW. Community-acquired pneumonia and hospital-acquired pneumonia. Med Clin North Am. 2019 May;103(3):487-501.

44. Mandell LA. Community-acquired pneumonia: An overview. Postgrad Med. 2015 Aug;127(6):607-615.

45. Wunderink RG, Waterer GW. Community-acquired pneumonia: pathophysiology and host factors with focus on possible new approaches to management of lower respiratory tract infections. Infect Dis Clin North Am. 2004 Dec;18(4):743-759.

46. Xue Y, Wang M, Han H. Interaction between alveolar macrophages and epithelial cells during Mycoplasma pneumoniae infection. Front Cell Infect Microbiol. 2023 Apr;13:1052020.

47. Jain V, Vashisht R, Yilmaz G, et al. Pneumonia pathology. Updated 2023 Jul 31. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 [Cited 2025 May 27]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526116/

48. Aliberti S, Dela Cruz CS, Amati F, Sotgiu G, Restrepo MI. Community-acquired pneumonia. Lancet. 2021 Sep 4;398(10303):906-919.

49. Ritchie AI, Wedzicha JA. Definition, causes, pathogenesis, and consequences of chronic obstructive pulmonary disease exacerbations. Clin Chest Med. 2020 Sep;41(3):421-438.

50. McLellan LK, Hunstad DA. Urinary tract infection: pathogenesis and outlook. Trends Mol Med. 2016 Nov;22(11):946-957.

51. Belyayeva M, Leslie SW, Rout P, et al. Acute pyelonephritis. Updated 2024 Feb 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 [Cited 2025 May 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519537/

52. Morello W, La Scola C, Alberici I, Montini G. Acute pyelonephritis in children. Pediatr Nephrol. 2016 Aug;31(8):1253-65.

53. Edwards B. Upper urinary tract infection (UUTI): pathogenesis and clinical findings [Internet]. Calgary (AB): The Calgary Guide to Understanding Disease; 2014 [Cited 2025 May 29]. Available from: https://calgaryguide.ucalgary.ca/upper-urinary-tract-infection-uuti-pathogenesis-and-clinical-findings/

54. Struyf T, Boon HA, van de Pol AC, Tournoy J, Schuermans A, Verheij TJM, Verbakel JY, Van den Bruel A. Diagnosing serious infections in older adults presenting to ambulatory care: a systematic review. Age Ageing. 2021 Feb 26;50(2):405-414.

55. Marchello CS, Ebell MH, Dale AP, Harvill ET, Shen Y, Whalen CC. Signs and symptoms that rule out community-acquired pneumonia in outpatient adults: a systematic review and meta-analysis. J Am Board Fam Med. 2019 Mar-Apr;32(2):234-247.

56. Htun TP, Sun Y, Chua HL, Pang J. Clinical features for diagnosis of pneumonia among adults in primary care setting: A systematic and meta-review. Sci Rep. 2019 May;9(1):7600.

57. Falk G, Fahey T. C-reactive protein and community-acquired pneumonia in ambulatory care: systematic review of diagnostic accuracy studies. Fam Pract. 2009 Feb;26(1):10-21.

58. Ebell MH, Bentivegna M, Cai X, Hulme C, Kearney M. Accuracy of biomarkers for the diagnosis of adult community-acquired pneumonia: a meta-analysis. Acad Emerg Med. 2020 Mar;27(3):195-206.

59. Contenti J, Occelli C, Lemoel F, Ferrari P, Levraut J. Presepsin versus other biomarkers to predict sepsis and septic shock in patients with infection defined by Sepsis-3 criteria: the PREDI study of diagnostic accuracy. Emergencias. 2019 Oct;31(5):311-317.

60. Gupta BK, Das BP, Mhaske VR, Tomar S, Rastogi K. Diagnostic accuracy of various biomarkers of sepsis (serum pro-calcitonin, high-sensitivity C-reactive protein, and C-reactive protein) and band cell percentage in critically ill patients: a prospective, observational, cohort study. Anesth Essays Res. 2020 Oct-Dec;14(4):615-619.