Australian Critical Care 32 (2019) 155–164

Contents lists available at ScienceDirect

Australian Critical Care

journal homepage: www.elsevier.com/locate/aucc

Review Paper

# A systematic review on risk factors associated with sepsis in patients admitted to intensive care units

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ARTICLE INFORMATION

*Article history:*
Received 31 October 2017
Received in revised form
29 January 2018
Accepted 5 February 2018

*Keywords:*
Sepsis
Intensive care unit
Health
Risk factor
Cohort
Case control

ABSTRACT

*Objective:* We sought to systematically review data on the risk factors influencing the incidence of sepsis in patients admitted to intensive care units (ICUs).
*Review methods:* An electronic search was undertaken in PubMed, MEDLINE, Scopus, and the Cochrane Library for studies reporting the risk factors of sepsis from the earliest available date up to December 30, 2016.
*Results:* Among the 2978 articles, 14 studies met the inclusion criteria with a total of 56 164 participants from nine countries. The extracted risk factors were from the following categories: demographic, critical care interventions, surgery-related factors, pre-existing comorbidities, severity of organ injury, and biomarkers and biochemical and molecular indicators. From demographic factors, older age and male gender were associated with an increased risk of sepsis among ICU-admitted patients.
*Conclusion:* Our analysis comprehensively summarised the risk factors of sepsis in patients admitted to medical, surgical, neurologic, trauma, and general ICUs. Age, sex, and comorbidities were non-modifiable risk factors; however, critical care interventions and surgery-related factors were modifiable factors and suggest that improving the care of surgical patients and effective management of critical care interventions may play a key role in decreasing the development of sepsis in patients admitted to the ICUs.


## 1. Introduction

Sepsis is the leading cause of mortality and critical illness worldwide.[1] The global incidence rate of hospital-treated sepsis was 437 cases per 100 000 person-years, with about 17% hospital mortality during the last decade.[1] The increasing rate of sepsis[2–4] is likely reflecting ageing populations with more comorbidities, greater recognition,[2,5] and, in some countries, reimbursement-favourable coding.[6] The initial definition of sepsis ("Sepsis-1") was developed by the American College of Chest Physicians and the Society of Critical-Care Medicine (SCCM) in 1992. Accordingly, sepsis was defined as a host's systemic inflammatory response syndrome (SIRS) to infection. Later, sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome began to be used in clinical practice.[7] In 2001, the second consensus meeting was held, and the diagnostic criteria for sepsis were expanded. Resultantly, "Sepsis-2" was developed in 2003.[8] In 2016, the SCCM and the European Society of Intensive Care Medicine generated the new definition for sepsis ("Sepsis-3").[2] Thus, sepsis is now defined as a life-threatening organ dysfunction caused by dysregulated host response to infection.[2]

Sepsis is a serious and growing medical problem among patients admitted to intensive care units (ICUs), with 17.3%–37.0% occurrences during ICU stays.[9–12] Because of limited treatment options, the prognosis of sepsis still remains poor with ICU mortality rates ranging from 36.0% to 55.2%.[9] Therefore, it is the most common cause of death in adult ICUs.[13–15] In this regard, the majority of

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https://doi.org/10.1016/j.aucc.2018.02.005
1036-7314/

sepsis studies have mainly focused on the acute management of the disease to reduce mortality rate[16–18]; however, in recent years, attention has been increasingly shifted towards identifying patients at risk of sepsis at admission.[16,19,20] A crude search in the literature shows that identifying risk factors for sepsis is a trending topic. In clinical settings, understanding risk factors is important in making medical decisions. It is essential for physicians to identify those patients at risk of sepsis to prevent subsequent complications and also to express treatment preferences. Several risk factors which may cause sepsis have been identified, including chronic medical conditions,[19] old age,[21] male gender,[22] alcoholism,[23] and immune suppression resulting from malignant diseases and their aggressive treatments.[13] Owing to the heterogeneous population of critically ill patients admitted to the ICUs, a wide variety of risk factors for the occurrence of sepsis have been reported in several studies over the years. Therefore, the objective of this systematic review was to pool the available data and summarise the risk factors associated with the incidence of sepsis in adult patients admitted to the ICUs during their ICU stay.

## 2. Methods

### 2.1. Systematic literature search

We performed a systematic literature search according to the commonly used guidelines for systematic reviews (PRISMA).[24] We searched MEDLINE, PubMed, Scopus, and the Cochrane Library for all potentially relevant studies from the earliest available date of indexing up to December 30, 2016, using a combination of the following keywords: (sepsis [MeSH Terms] OR infection [Text Word] OR nosocomial infection [MeSH Terms]) AND (intensive care unit*[MeSH Terms] OR ICU [Text Word] AND risk factor*[MeSH Terms]) AND (cohort study [MeSH Terms] OR case control study [MeSH Terms] OR prospective study [MeSH Terms]). We also manually searched additional studies in the reference lists of all included publications. However, we did not retrieve the conference literature, grey literature, and unpublished literature to enhance the scientific rigour of research. The detailed search strategies are presented in Supplementary file 1.

### 2.2. Eligibility criteria

Since our search was limited to publications before 2016, the included studies used different criteria to define sepsis, including International Classification of Diseases, Centers for Disease Control and Prevention, Sepsis-1, and Sepsis-2. In the present review, we focused on studies that examined the risk factors for sepsis in adult patients, aged ≥18 years who met the following inclusion criteria: (1) all patients who were transferred to general, surgical, anaesthesiology, neurosurgery, cardiac surgery, and medical ICUs from other hospitals or other wards within the hospital, (2) patients without sepsis at admission, according to the aforementioned sepsis criteria, and (3) patients who stayed in the ICU for over 48 h. The outcome of interest was the occurrence of sepsis at least after 24 h of ICU admission. We excluded studies where the outcome was severe sepsis or septic shock. Studies were included in our review if the study design was either cohort (prospective or retrospective) or case–control. We excluded cross-sectional design studies, also known as prevalence studies, because in this type of studies the presence of risk factors and outcomes is measured simultaneously, and it may be difficult to determine whether the exposure or the disease came first and also to assess the cause and effect relationship.[25,26] We accepted studies which were published in English whose full texts were available for the present review. Eligible studies had to be published as full-length articles in peer-reviewed journals.

### 2.3. Data extraction and quality assessment

After reviewing the retrieved titles, two authors independently reviewed the abstracts to include the relevant articles and subsequently extracted the following information from each article and entered it on an Excel spreadsheet: first author's name, year of publication, country, details of the study design, type of ICU, type of hospital, characteristics of the patients (age, sex), numbers of patients enrolled to the study, duration of study, study outcomes, method of diagnosing of sepsis, identified risk factors and their adjusted effect size (odds ratio [OR], relative risk, and mean difference), and methods of analysis. The authors independently evaluated the methodological quality of eligible studies using a 9-star system by Newcastle–Ottawa Scale.[27] All studies were given a score between 0 and 9 points by two authors. Studies with the score of ≥7 were considered as high quality in methodology; scores between 4 and 6 were considered as moderate quality and scores between 0 and 3 as low quality. Discrepancies between the two reviewers were solved by having a third author review to reach consensus.

## 3. Results

### 3.1. Search results

We found 372 articles from MEDLINE, 1039 from PubMed, 1973 from Scopus, and 35 from Cochrane Library. These searches were combined and duplicates were removed. Fig. 1 depicts the flow of the study selection process. We scanned 2978 titles and selected 343 abstracts for review. Then 17 articles were selected for full-text review. The reference lists of these full-text articles yielded six additional studies; hence, we retrieved 23 full-text articles. After full review of these articles, we excluded nine of them as they did not meet all inclusion criteria. The main reasons for exclusion were (i) sepsis was not the main outcome (n = 1), (ii) patients were not ICU-admitted (n = 1), (iii) analysis was done only for prediction purposes (n = 1), (iv) the study was cross-sectional (n = 2), (v) the sepsis was community-acquired sepsis (n = 1), (vi) no significant risk factor was found (n = 2), and (vii) for one study sample size was very low (n = 1). Finally, of the 23 full-text articles, 14 met our inclusion criteria.

### 3.2. Qualitative summary

The methodological and clinical characteristics, as well as the main results of studies included, are summarised in Tables 1–3. We retrieved 14 studies that enrolled a total of 56 164 participants from nine countries. There were 1781 participants from six prospective cohort studies, 53 777 participants from five retrospective cohort studies, and 666 participants from three case–control studies. The included studies were conducted in Croatia, Austria, Germany, United States of America (USA), United Kingdom (UK), Brazil, France, Greece, and Spain. The follow-up duration of the studies ranged from 4 months to 16 years. The mean age of the study participants ranged from 34 to 71.7 years, and the male percentage ranged from 30% to 100%. Table 1 and Supplementary Table 1 summarise the NOS of included studies. The majority of those studies were of high quality. Only two prospective cohort (scores of 3 and 5) and one case–control studies (score of 3) did not show acceptable selection criteria and comparability between groups. Most of the studies were conducted in university hospitals.

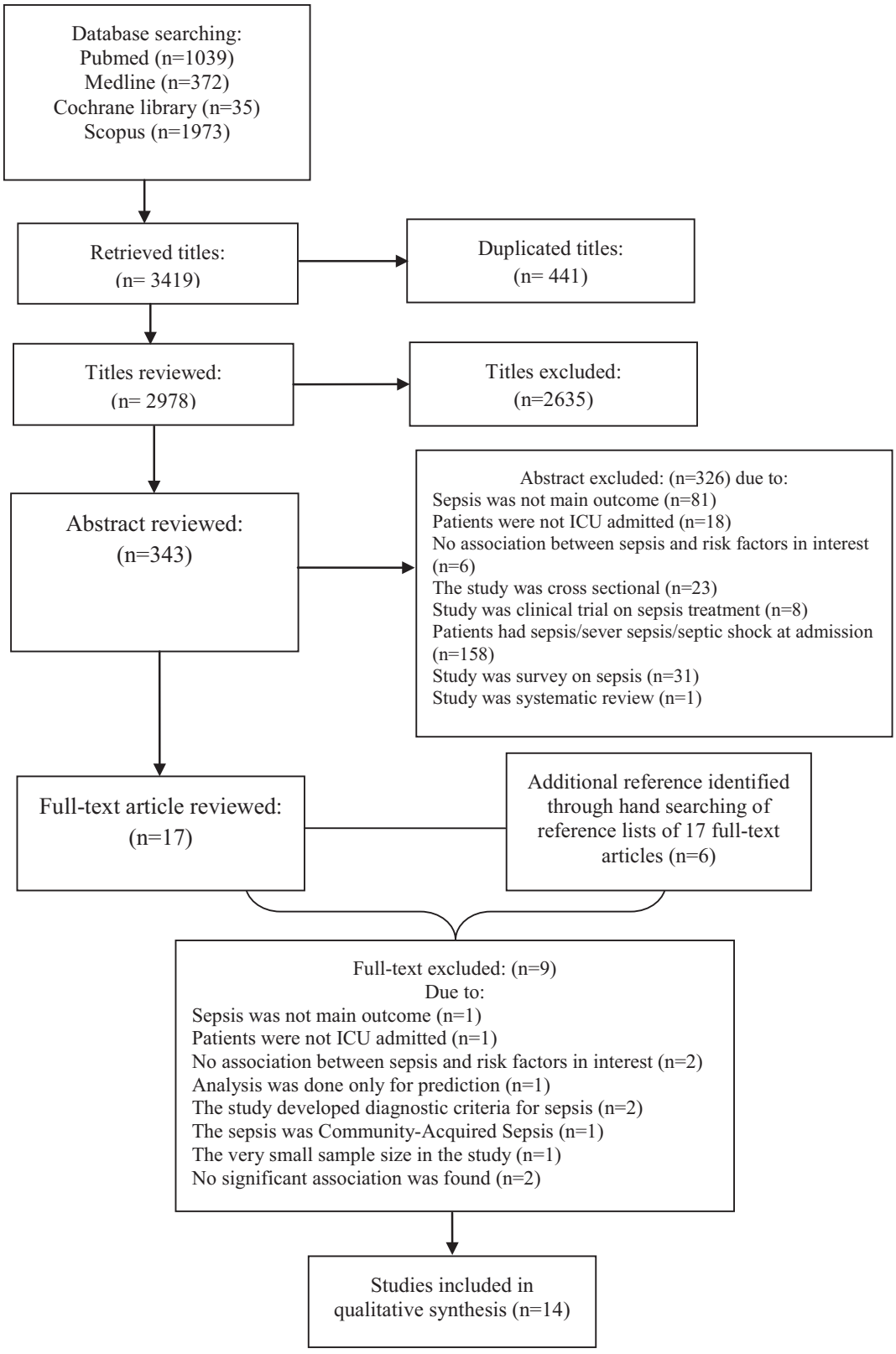


**Fig. 1.** Flowchart of the systematic review of risk factors associated with sepsis in patients admitted to intensive care units.

Critically ill patients were admitted to medical, surgical, neurologic, trauma, and general ICUs.

Most of the included studies used the SIRS criteria of the SCCM[7] for definition of sepsis. Two studies used the criteria of International Classification of Diseases, 9th Edition,[28] one study used standard definitions of the Centers for Disease Control and Prevention,[29] and one study used the criteria of German Sepsis Society for definition of sepsis.[30] Crude rates of post-operative

**Table 1**
Characteristics of studies included in the systematic review.

| First author | Year | Country | Study design | Duration of study | Participant number | Age (year) | Sex, male (%) | Newcastle–Ottawa Scale |
|---|---|---|---|---|---|---|---|---|
| Baršić[21] | 1999 | Croatia | Prospective cohort | 7 years | 660 | 50.5 | 61% | 8 |
| Geppert[35] | 2000 | Austria | Case–control | NA | 25 cases/7 control | 59 | 100% | 3 |
| Hubacek[39] | 2001 | Germany | Case–control | NA | 204 cases/250 control | 55 | 55% | 3 |
| Dahl[36] | 2003 | USA | Prospective cohort | 4 months | 98 | 34 | 72% | 8 |
| O'Brien Jr[23] | 2007 | USA | Retrospective cohort | 5 years | 9981 | 48.3 | 66% | 8 |
| Hampshire[58] | 2011 | UK | Prospective study | NA | 92 | 66 | 74% | 8 |
| Wafaisade[22] | 2011 | Germany | Retrospective study | 16 years | 29 829 | 42 | 72.5% | 7 |
| Elias[33] | 2012 | Brazil | Prospective cohort | 3 years | 625 | 53.1 | 56.3% | 8 |
| Berger[13] | 2014 | Germany | Retrospective cohort | 2 years | 238 | 64.5 | 68.5% | 9 |
| Lagrost[38] | 2014 | France | Prospective cohort | 1 year | 217 | 71.7 | 68.2% | 5 |
| Trentzsch[31] | 2014 | Germany | Retrospective cohort | 5 years | 10 343 | 44 | 73.2% | 7 |
| Vassiliou[37] | 2014 | Greece | Prospective cohort | 2 years | 89 | 46 | 30% | 8 |
| Moromizato[32] | 2014 | USA | Retrospective cohort | 13 years | 3386 | 65.9 | 44% | 8 |
| Fariñas-Alvarez[34] | 2000 | Spain | Case–control | 1 year | 90 case/90 control | 60.2 | 73% | 9 |

sepsis, calculated by dividing the number of patients developed sepsis by the number of all patients, ranged from 7 to 50.5%, as reported in 11 cohort studies.

### 3.3. Factors associated with sepsis at ICU

Tables 3 and 4 summarise the effect sizes and results of statistical tests of major risk factors from the following categories: demographic, critical care interventions, surgery-related factors, comorbidity, severity of organ injury, and biomarkers and biochemical and molecular indicators. A detailed description of these risk factors is given below.

### 3.4. Demographic characteristic

The effects for gender were examined in 10 cohort studies; however, only three studies[22,31,32] showed a significant association between sepsis and male gender in multivariable analysis: OR: 1.81 ($p < 0.001$), OR: 1.55 ($p < 0.001$), and OR: 1.20 ($p = 0.05$), respectively. Also, all the 11 cohort studies assessed the influence of age on the incidence of sepsis in critically ill patients. Only two studies reported a significant association between older age and incident sepsis in ICU-admitted patients[21,22] (OR: 1.62 [$p < 0.001$] and OR: 1.09 [$p < 0.01$]), and one study showed negative or inverse association between age and incident sepsis (OR: 0.99 [$p < 0.001$]).[32]

### 3.5. Critical care interventions

A positive association between mechanical ventilation during ICU stay was reported in two cohort studies[21,33] (OR: 1.20 [$p < 0.05$] and OR: 5.51 [ $p < 0.001$], respectively). Other invasive procedures such as urinary catheters and central venous catheters were positively associated (OR: 1.49 [$p < 0.001$] and OR: 1.19 [$p < 0.001$]) with sepsis according to one cohort study.[21] Also, one case–control study reported a positive association (OR: 5.1 [$p < 0.001$]) between incident sepsis and use of nasogastric tubes for parenteral nutrition in critically ill patients.[34] Therapeutic interventions such as fluid resuscitation and use of vasoactive drugs were also found as risk factors (OR: 1.90 [$p < 0.01$] and OR: 2.58 [$p < 0.001$]) for the occurrence of sepsis in a cohort study.[33]

### 3.6. Surgery-related factors

Urgent or emergency surgeries were identified as risk factors associated with sepsis in one case–control[34] and one cohort study.[33] The adjusted ORs were 3.0 ($p < 0.001$) and 2.63 ($p < 0.001$), respectively. Two cohort studies reported a positive association between sepsis incidence and the number of surgical interventions[34] and the number of operative procedures,[22] with adjusted ORs of 2.5 ($p < 0.001$) and 2.37 ($p < 0.001$), respectively.

Abdominal surgery[34] and laparotomy[22] were identified as independent risk factors for the development of sepsis in two case–control (OR: 2.6, $p < 0.001$) and cohort studies (OR: 1.18, $p < 0.01$), respectively. One cohort study reported a measure of association (OR: 1.60, $p < 0.001$) between the number of packed red blood cells transfused between emergency room arrival and ICU admission.[22]

### 3.7. Pre-existing comorbidities

Several studies have assessed the effect of pre-existing comorbidities on the development of sepsis in ICU-admitted patients.[13,21–23,34] Pre-existing medical conditions were shown as risk factors in two studies, one cohort[22] and one case–control.[34] In the case–control study,[34] it was shown that two or more intrinsic comorbidities were associated with increased odds of sepsis (OR: 11.8, $p < 0.001$), and the cohort study[22] reported the increased risk for sepsis in patients with pre-existing medical conditions (OR: 1.62, $p < 0.001$). Chronic obstructive pulmonary disease (COPD), immunosuppressive disorders,[13] and alcohol dependence[23] have also been identified as risk factors for sepsis development, with adjusted ORs of 3.81 ($p < 0.05$), 18.47 ($p < 0.05$), and 1.54 ($p < 0.001$), respectively.

Two cohort studies have assessed the predictive role of two ICU scoring systems including Glasgow Coma Scale[22] and the Simplified Acute Physiology Score II[13] that provide the status for the central nervous system (CNS) and morbidity score for a critically ill patient. Those studies reported a positive association between sepsis incidence and Glasgow Coma Scale <8 (OR: 1.32, $p < 0.001$) and one unit increase in the Simplified Acute Physiology Score II (OR: 1.09, $p < 0.01$). Coma[34] and CNS infection at ICU admission[21] were reported as two risk factors, with ORs of 13.5 ($p < 0.001$) and 1.14 ($p < 0.001$), respectively.

### 3.8. Severity of organ injury

One cohort study[22] reported the significant association between severity of organ injury in traumatic patients and sepsis incidence, which were measured by the number of injuries (OR: 1.09, $p < 0.001$), injury severity score (OR: 1.01, $p < 0.001$), abbreviated injury scale (THORAX) score (OR: 1.30, $p < 0.001$).

**Table 2**
Characteristic of hospitals and ICUs, the study end points, and identified risk factors of sepsis according to the studies included in the systematic review.

| First author | Year | Type of hospital | Type of ICU | Study end points | Criteria for diagnosis of sepsis | Incidence of sepsis | Risk factors |
|---|---|---|---|---|---|---|---|
| Baršić[21] | 1999 | University hospital | Medical | Sepsis, pneumonia, and urinary tract infection | Standard definitions of the Centers for Disease Control and Prevention | 20.3% | Age; length of mechanical ventilation; duration of central venous; catheter and urinary catheter use; and diagnosis of central nervous system infection on admission |
| Geppert[35] | 2000 | University hospitals | General | Presence of SIRS, later development of septic complications, and ICU-survival | Presence of two criteria of SIRS and a positive blood culture, a positive bacterial isolate from urine, or a tracheobronchial aspirate together with radiologic signs compatible with pneumonia. | NA | sP-selectin |
| Hubacek[39] | 2001 | Trauma centre | Trauma | Sepsis | SIRS | NA | Polymorphisms in the gene for lipopolysaccharide binding protein in combination to male gender |
| Dahl[36] | 2003 | University hospitals and trauma Centre | Surgical | Postinjury organ dysfunction, severe sepsis, and sepsis | SIRS and positive microbiological culture | 21% | Low level of circulating levels of Gc-globulin at admission |
| O'Brien Jr[23] | 2007 | University hospitals | Medical/ surgical | Sepsis, septic shock, hospital mortality, and length of stay | ICD-9 | 8.23% | Alcohol dependence |
| Hampshire[58] | 2011 | Trauma centres | Medical/ surgical | Sepsis | SIRS criteria, laboratory results, radiographs, and computed tomography scan | 27% | Duration of surgery |
| Wafaisade[22] | 2011 | University hospital | Trauma | Post-traumatic sepsis | SIRS | 10.20% | Male gender; age; pre-existing medical condition; Glasgow Coma scale score of <8 at scene; injury severity score; abbreviated injury scale (THORAX) score of >3; number of injuries; number of red blood cell units transfused; number of operative procedures; and laparotomy |
| Elias[33] | 2012 | University hospital | Surgical | Infection and sepsis | SIRS | 9% | Urgent surgeries; mechanical ventilation; fluid resuscitation; and vasoactive drugs in the post-operative period |
| Berger[13] | 2014 | University hospital | Neurologic | Sepsis, mortality | German Sepsis Society | 12.6% | Immunosuppressive disorders; chronic obstructive pulmonary disease; and the simplified acute physiology score (SAPS II) at admission |
| Lagrost[38] | 2014 | Trauma centre | Surgical | SIRS and sepsis | SIRS and positive culture samples at any site and at any time during the ICU stay | 7% | Low plasma cholesterol concentration at baseline |
| Trentzsch[31] | 2014 | University hospital | General | Multiple organ failure, sepsis, and mortality | SIRS | 14% | Male gender |
| Vassiliou[37] | 2014 | University hospital | General | Sepsis | SIRS and result of documented infection | 50.56% | Increased level of sE- and sP-selectin |
| Moromizato[32] | 2014 | Tertiary care centre | Medical/ surgical | Sepsis and mortality | ICD-9 and SIRS | 16.8 | Deficiency in 25-hydroxy vitamin D, male gender, and age |
| Fariñas-Alvarez[34] | 2000 | University hospital | Surgical | Sepsis | SIRS | NA | Coma within 48 h before sepsis; low serum albumin level at admission; two or more intrinsic comorbidities; parenteral nutrition; emergency surgery; abdominal surgery; and number of surgical interventions |

ICD-9 = International Classification of Diseases, 9th Edition; SIRS = systemic inflammatory response syndrome; NA = not applicable; ICU = intensive care unit.

**Table 3**
Identified risk factors with their adjusted effect sizes for sepsis development.

| First author | Year | Risk factors of sepsis (effect size) | Statistical method | Measure of effect size |
|---|---|---|---|---|
| Baršić[21] | 1999 | Duration of urinary catheterisation (0.401), diagnosis of CNS infection at admission (0.131), duration of the use of central venous catheters (0.182), age (0.089), and duration of mechanical ventilation (0.185) | Multivariable logistic regression | Beta |
| Geppert[35] | 2000 | sP-selectin (350.2 ± 233.4 ng/ml vs. 158.5 ± 157.8 ng/ml) | t-test | Mean difference |
| Hubacek[39] | 2001 | Polymorphisms in the gene for lipopolysaccharide binding protein in combination to male gender (3%) | Chi-square | Frequency |
| Dahl[36] | 2003 | Low level of circulating levels of Gc-globulin at admission (na) | Multivariate logistic regression | OR |
| O'Brien Jr[23] | 2007 | Alcohol dependence (1.54) | Multivariate logistic regression | OR |
| Hampshire[58] | 2011 | Duration of surgery (1.2) | Multivariate logistic regression, | OR |
| Wafaisade[22] | 2011 | Male gender (1.81); age (1.62); preexisting medical condition (1.62); Glasgow Coma Scale score of <8 at scene (1.32); injury severity score (1.01); abbreviated injury scale (THORAX) score of >3 (1.30); number of injuries (1.60); number of packed red blood cell units transfused (1.60); number of operative procedures (2.37); and laparotomy (1.18) | Multivariate logistic regression | OR |
| Elias[33] | 2012 | Urgent surgeries (2.63); mechanical ventilation (5.51); fluid resuscitation (1.90); and vasoactive drugs in the post-operative period (2.58) | Multivariate logistic regression, | OR |
| Berger[13] | 2014 | Immunosuppressive disorders (18.47); chronic obstructive pulmonary disease (3.81); and the simplified acute physiology score at admission (1.09) | Multivariate logistic regression | OR |
| Lagrost[38] | 2014 | Low plasma cholesterol concentration at baseline (pre-operation) (occurrence 18.6% in patient with baseline cholesterol of 1.23 g/l) | Univariate analysis | Frequency |
| Trentzsch[31] | 2014 | Male gender (1.55) | Univariate analysis | OR |
| Vassiliou[37] | 2014 | Increased level of sE (1.03)- and sP-selectin (1.08) | Multivariate Cox regression | RR |
| Moromizato[32] | 2014 | Deficiency in 25-hydroxy-vitamin D (1.63) | Multivariate logistic regression | OR |
| Fariñas-Alvarez[34] | 2000 | Coma within 48 h before sepsis; low serum albumin level at admission (<40 mg/dl); two or more intrinsic comorbidities; parenteral nutrition; emergency surgery; abdominal surgery; and number of surgical interventions | Multivariate logistic regression | OR |

CNS = central nervous system; OR = odds ratio; RR = relative risk.

### 3.9. Biomarkers and biochemical and molecular indicators

Three biomarkers including sP-selectin, sE-selectin, and Gc-globulin have been assessed in one case–control[35] and two prospective studies.[36,37] Also, three biochemical indicators including serum albumin, plasma cholesterol, and serum 25-hydroxy-vitamin D have been studied separately in one case–control[34] and two cohort studies,[32,38] respectively. The effect size for the aforementioned indicators has been presented in Table 4. Additionally, one case–control study showed that common polymorphisms in the gene for lipopolysaccharide binding protein in combination with male gender are associated with an increased risk for the development of sepsis (Table 4).[39]

## 4. Discussion

To the best of our knowledge, this study is the first systematic review for the risk factors of sepsis in patients admitted to the ICUs. About 3000 titles were reviewed to identify 14 manuscripts with sufficient quality to identify risk factors for sepsis. The average score of the studies according to NOS was 7.6 for the 11 cohort studies and 5 for the three case–control studies, indicating a low risk of bias in the included cohort studies and a moderate risk of bias of the included case–control studies. The investigations included in this review incorporate more than 56 000 patient admissions from diverse ICUs. A broad range of risk factors, including demographic, critical care interventions, surgery-related factors, comorbidity, severity of organ injury, and biomarkers and biochemical and molecular indicators were extracted from eligible articles.

Among the cohort studies included in our review, two studies reported positive[21,22] and one study reported negative association[32] between age and incident sepsis. It has been shown that the elderly are at particular risk for sepsis, accounting for nearly two-thirds of all patients hospitalised with sepsis in the United States, in 2008.[40] The reasons for increased incidence among the elderly are multifactorial, including diminished physiologic reserve, immunosenescence, subtle clinical presentations, frequent use of invasive instruments, and hospitalisation.[41] Also, the presence of at least one comorbid conditions such as coronary artery disease, congestive heart failure, and COPD is common in patients older than 65 years,[40,42] which predispose elderly to sepsis.[40] According to epidemiological studies, almost 60% of sepsis occurs in patients aged 65 years or older.[9,28,40] The ageing of the population probably explains the increasing incidence of sepsis in industrialised countries.[40]

Among 11 cohort studies included in our review, three studies found a significant association between male gender and sepsis after adjustment for confounders.[22,31,32] Numerous experimental and clinical studies have shown a greater incidence of sepsis in men, ranging from 54% to 66%.[9,11,43] This association has remained unexplained but may imply the effect of female sex hormones on immunity and on cardiovascular response.[44]

Three studies investigated the association between invasive procedures used during an ICU stay and incidence of sepsis.[21,33,34] Among these procedures, mechanical ventilation was reported as

**Table 4**
Identified risk factors for sepsis according to the studies included in the systematic review.

| Risk factor category | Variables | First author | Year | Study end points | Definition of the risk factor | Effect size | Confidence interval | p-value | Measure of effect size |
|---|---|---|---|---|---|---|---|---|---|
| Demographic | Age | Baršić[21] | 1999 | Sepsis, pneumonia, and urinary tract infection | Age (1 year) | 1.09 | – | 0.002 | OR |
| | Age | Wafaisade[22] | 2011 | Post-traumatic sepsis | Age (1 year) | 1.62 | (1.45–1.80) | <0.001 | OR |
| | Age | Moromizato[32] | 2014 | Sepsis and mortality | Age (1 year) | 0.99 | (0.98–1.00) | p < 0.001 | OR |
| | Male gender | Wafaisade[22] | 2011 | Post-traumatic sepsis | Male vs. female | 1.81 | (1.61–2.03) | p < 0.001 | OR |
| | Male gender | Trentzsch[31] | 2014 | Multiple organ failure, sepsis, and mortality | Male vs. female | 1.55 | (1.35–1.77), | p < 0.001 | OR |
| | Male gender | Moromizato[32] | 2014 | Sepsis and mortality | Male vs. female | 1.20 | (1.00–1.44) | 0.05 | OR |
| Critical care interventions | Duration of urinary catheterisation | Baršić[21] | 1999 | Sepsis, pneumonia, and urinary tract infection | Number of urinary catheter days | 1.49 | – | <0.001 | OR |
| | Duration of the use of central venous catheters | Baršić[21] | 1999 | Sepsis, pneumonia, and urinary tract infection | Number of central venous catheters days | 1.19 | – | <0.001 | OR |
| | Duration of mechanical ventilation | Baršić[21] | 1999 | Sepsis, pneumonia, and urinary tract infection | Number of mechanical ventilation days | 1.20 | – | 0.026 | OR |
| | Mechanical ventilation | Elias[33] | 2012 | Infection and sepsis | Mechanical ventilation (vs. no) | 5.51 | (3.07–9.89) | <0.001 | OR |
| | Parenteral nutrition | Fariñas-Alvarez[34] | 2000 | Sepsis | Parenteral nutrition | 5.1 | (1.5–17.1) | p < 0.001 | OR |
| | Vasoactive drugs in the post-operative period | Elias[33] | 2012 | Infection and sepsis | Vasoactive drugs in the postoperative period (vs. no) | 2.58 | (1.61–4.14) | <0.001 | OR |
| | Fluid resuscitation | Elias[33] | 2012 | Infection and sepsis | Fluid resuscitation (vs. no) | 1.90 | (1.18–3.05) | 0.008 | OR |
| Surgery-related factors | Emergency surgery | Fariñas-Alvarez[34] | 2000 | Sepsis | Emergency surgery (vs. no) | 3.0 | (1.4–6.4) | p < 0.001 | OR |
| | Urgent surgeries | Elias[33] | 2012 | Infection and sepsis | Urgent surgeries (vs. Elective) | 2.63 | (1.50–4.63) | <0.001 | OR |
| | Abdominal surgery | Fariñas-Alvarez[34] | 2000 | Sepsis | Abdominal surgery (vs. no) | 2.6 | (1.0–6.8) | p < 0.001 | OR |
| | Laparotomy | Wafaisade[22] | 2011 | Post-traumatic sepsis | Laparotomy (vs. no laparotomy) | 1.18 | (1.05–1.32) | 0.007 | OR |
| | Number of surgical interventions | Fariñas-Alvarez[34] | 2000 | Sepsis | Number of surgical interventions (≥2 vs. 0) | 2.5 | (1.1–6.1) | p < 0.001 | OR |
| | Number of operative procedures | Wafaisade[22] | 2011 | Post-traumatic sepsis | Number of operative procedures ≥2 vs. 0 | 2.37 | (1.98–2.83) | <0.001 | OR |
| | Duration of surgery | Hampshire[58] | 2011 | Sepsis | Duration of surgery (hours) | 1.2 | (0.991.44) | 0.054 | OR |
| | Number of red blood cell units transfused | Wafaisade[22] | 2011 | Post-traumatic sepsis | Number of packed red blood cell transfused units ≥10 vs. 0 | 1.60 | (1.37–1.88) | <0.001 | OR |
| Comorbidities | Diagnosis of CNS infection at admission | Baršić[21] | 1999 | Sepsis, pneumonia, urinary tract infection | Diagnosis of CNS infection based on symptoms and signs of the illness and the examination of the cerebrospinal fluid | 1.14 | – | <0.001 | OR |
| | Coma within 48 h before sepsis | Fariñas-Alvarez[34] | 2000 | Sepsis | Coma within 48 h before sepsis (vs. no) | 13.5 | (3.6–50.8) | p < 0.001 | OR |
| | Glasgow Coma Scale score | Wafaisade[22] | 2011 | Post-traumatic sepsis | Glasgow Coma Scale score of <8 at scene (vs. ≥8) | 1.32 | (1.19–1.46) | <0.001 | OR |
| | Intrinsic comorbidities | Fariñas-Alvarez[34] | 2000 | Sepsis | Intrinsic comorbidities (≥2 vs. 0) | 11.8 | (2.8–49.4) | p < 0.001 | OR |
| | Pre-existing medical condition | Wafaisade[22] | 2011 | Post-traumatic sepsis | Pre-existing medical condition (vs. none) | 1.62 | (1.45–1.80) | <0.001 | OR |
| | Chronic obstructive pulmonary disease | Berger[13] | 2014 | Sepsis and mortality | Chronic obstructive pulmonary disease (vs. no) | 3.81 | (1.33–10.86) | 0.012 | OR |
| | Immunosuppressive disorders | Berger[13] | 2014 | Sepsis and mortality | Immunosuppressive disorders (vs. no) | 18.47 | (1.38–247.91) | 0.028 | OR |
| | The simplified acute physiology score (SAPS II) at admission | Berger[13] | 2014 | Sepsis and mortality | The simplified acute physiology score (SAPS II) at admission (1 score) | 1.09 | (1.04–1.14) | 0.002 | OR |
| | Alcohol dependence | O'Brien Jr[23] | 2007 | Sepsis, septic shock, hospital mortality, and length of stay | Alcohol dependence based on ICD-9 codes in the discharge record | 1.54 | – | <0.001 | OR |
| Severity of organ injury | Number of injuries | Wafaisade[22] | 2011 | Post-traumatic sepsis | Number of injuries (per 1) | 1.09 | (1.07–1.11) | <0.001 | OR |
| | Injury severity score | Wafaisade[22] | 2011 | Post-traumatic sepsis | Injury severity score (points) | 1.01 | (1.01–1.02) | <0.001 | OR |
| | Abbreviated Injury Scale (THORAX) score | Wafaisade[22] | 2011 | Post-traumatic sepsis | Abbreviated Injury Scale (THORAX) score of >3 (vs. ≤3) | 1.30 | (1.17–1.45) | <0.001 | OR |

(*continued on next page*)

**Table 4** (*continued*)

| Risk factor category | Variables | First author | Year | Study end points | Definition of the risk factor | Effect size | Confidence interval | p-value | Measure of effect size |
|---|---|---|---|---|---|---|---|---|---|
| Biomarkers | sP-selectin | Geppert[35] | 2000 | Presence of SIRS, later development of septic complications, and ICU-survival | Soluble Forms of P-selectin in plasma | 350.2 ng/mL | – | 0.022 | Mean |
| | Low level of Circulating levels of Gc-globulin at admission | Dahl[36] | 2003 | Postinjury organ dysfunction, severe sepsis, and sepsis | Plasma Gc-globulin≤134 mg/L at admission | NA | | 0.006 | OR |
| | Increased level of sE-selectin | Vassiliou[37] | 2014 | Sepsis | Increased level of sE-selectin (ng/ml) (by 10 units) | 1.03 | (1.02–1.05) | p < 0.001 | RR |
| | Increased level of sP-selectin | Vassiliou[37] | 2014 | Sepsis | Increased level of sP-selectin (ng/ml) (by 10 units) | 1.08 | (1.04–1.14) | p < 0.001 | RR |
| Biochemical indicators | Low serum albumin level at admission (<40 mg/dl) | Fariñas-Alvarez[34] | 2000 | Sepsis | Low serum albumin level at admission (<35 vs. >39 mg/dl) | 15.8 | (5.4–46.4) | p < 0.001 | OR |
| | Low plasma cholesterol concentration at baseline | Lagrost[38] | 2014 | SIRS and sepsis | Low plasma cholesterol concentration at baseline (<1.23 g/L) | 18.6% | – | 0.005 | Frequency |
| | Deficiency in 25-hydroxy-vitamin D | Moromizato[32] | 2014 | Sepsis and mortality | Deficiency in 25-hydroxy-vitamin D (≤15 vs. ≥ 30 ng/Ml) | 1.63 | (1.27–2.08) | p < 0.001 | OR |
| Molecular indicators | Polymorphisms in the gene for lipopolysaccharide binding protein in combination to male gender | Hubacek[39] | 2001 | Sepsis | Polymorphisms in lipopolysaccharide binding protein (Cys98→Gly; Pro436→Leu) | 3% | – | <0.02 | Frequency |

CNS = central nervous system; OR = odds ratio; RR = relative risk; ICD-9 = International Classification of Diseases, 9th Edition; SIRS = systemic inflammatory response syndrome.

a risk factor in two studies.[21,33] This was probably associated with the high frequency of the development of ventilator-associated pneumonia as the site of infection in critically ill patients.[45] Because mechanical ventilation is a modifiable risk factor, decreasing the duration of mechanical ventilation using quality-improvement programs in surgical patients may play a key role in decreasing sepsis development. Other invasive procedures such as different types of catheters used during ICU stay and the duration of catheterisation were reported as risk factors in the three aforementioned studies. Catheter-related bloodstream infections are common in ICUs and potentially lethal.[46] According to the National Nosocomial Infections Surveillance system, the median rate of catheter-related bloodstream infection in ICUs of all types ranged from 1.8 to 5.2 per 1000 catheter-days during 1992–2004.[47] Therefore, effective management of tube system can reduce infection rate and improve outcome.

A large number of risk factors identified in our review were related to the surgery. Surgical patients are vulnerable to infectious complications during hospitalisation because of several factors such as old age, pre-existing medical conditions, and prolonged periods of hospitalisation.[33] In one cohort study with a large sample[33] and one case–control study,[34] emergency surgery was identified as a significant and powerful predictor for sepsis in surgical patients admitted to the ICU. Several studies have shown that unplanned surgeries were predictors for some complications in the post-operative period.[48,49]

Two studies included in our review showed that laparotomy and abdominal surgery were predictors of sepsis in surgical patients admitted to the ICU. A recently systematic review study has reported that the morbidity of non-therapeutic laparotomy can be as high as 33.3% and is related to pulmonary problems, wound infections, post-operative ileus, and ventral hernia.[50]

Findings from five studies included in our review showed that comorbidities such as COPD,[13] immunosuppressive disorders,[13] CNS infection,[21] and alcohol dependence increased the risk of sepsis in patients admitted to the ICU. Current studies show that more than 50% of patients with severe sepsis present at least one comorbid illness.[9,51] Diabetes mellitus, congestive heart failure, chronic pulmonary disease, immunosuppression, liver disease, cancer, and chronic renal failure have been associated with sepsis.[52,53]

Recently, several biomarkers have received increasing attention in distinguishing between sepsis and non-septic patients fulfilling the SIRS criteria.[54] Leukocyte–endothelium interactions are pivotal events in the development and progression of sepsis[35,54]; these interactions are facilitated by soluble form of selectins, a family of cell adhesion molecules.[55] Among the included studies in our review, one prospective controlled study[35] showed that sP-selectin levels were higher in patients developing sepsis within 1 week after cardiopulmonary resuscitation than in patients without sepsis; however, the adjustment for confounders was not performed in that study. Another study[37] showed that increased levels of sE- and sP-selectin were related to sepsis development in patients admitted to a general ICU after adjustment for confounders.

One study included in our review showed that deficiency in 25-hydroxy-vitamin D was a predictor of sepsis in patients admitted to the ICUs. Although that study included insufficient sample size, a systematic review and meta-analysis have reported a significant association between vitamin D deficiency and increased susceptibility of sepsis.[56] Although extensive researches on sepsis biomarkers have been conducted in the last decades,[57] a singular ideal biomarker has not yet been identified. Hence, this field shows great potential for knowledge expansion in the near future.

Our study had a number of limitations. First, most of the studies included in our review were done in university hospitals, which

may not reflect patient populations at other types of medical centres. Second, retrieved studies were heterogeneous regarding the ICU types, definitions of sepsis, adjusted covariates, and sample size; as such, the comparison of studies was difficult. And last but not least, included studies were observational because this systematic review was designed to identify risk factors for sepsis. Therefore, the conclusion of this study may be influenced by the bias of observational studies. Nevertheless, the majority of the included studies had good quality as assessed using the Newcastle–Ottawa Scale.

## 5. Conclusion

Several risk factors of sepsis have been identified and investigated in recent years, and most of them have been revealed in at least two studies and can, therefore, be routinely employed in clinical practice. Some critical care interventions and surgery-related factors were modifiable risk factors and suggest that a considerable percentage of sepsis cases may be prevented through widespread quality-improvement programs such as decreasing the duration of mechanical ventilation in surgical patients, effective management of tube systems, and treatment of some metabolic disorders during ICU stay.

## Ethical approval

Ethical approval was not required in this study.

## Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Author contributions

AR and MF designed the study and revised the manuscript. NMM and MF worked equally in study selection, data collection, and drafted the manuscript. AR and MF assessed the quality of included studies. All authors reviewed and approved the final manuscript.

## Supplementary information

Supplementary data related to this article can be found at https://doi.org/10.1016/j.aucc.2018.02.005.

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