Turk J Gastroenterol *2016; 27: 458-63*

Effect of SIRS and sepsis on mortality in alcoholic hepatitis: A systematic review and meta-analysis

LIVER

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Original Article

ABSTRACT

Background/Aims: Sepsis is frequently observed in patients with alcoholic hepatitis (AH) and is an important mortality predictor. Several studies have also identified systemic inflammatory response syndrome (SIRS) as a significant prognostic factor. The aim of this study was to systematically review and quantify the effect of SIRS and sepsis on mortality in patients with AH.

Materials and Methods: MEDLINE and EMBASE were searched from its inception till January 2016. Participants in the included studies were adults with AH and those with developed SIRS or sepsis during hospitalization. We estimated the risk ratio (RR) with a 95% confidence interval (CI) of mortality by comparing participants with SIRS vs. non-SIRS and sepsis vs. non-sepsis.

Results: Data were extracted from six studies involving 1,264 patients (of whom 507 had SIRS) and four studies involving 57,529 patients (of whom 1,449 had sepsis). SIRS and sepsis were both significantly associated with mortality with RRs of 2.7 (95% CI 1.74–4.14, I2=50%) and 2.8 (95% CI 1.58–4.93, I2=94%), respectively.

Conclusion: Not only is sepsis associated with mortality but also SIRS. SIRS may be the initial trigger of cascade events leading to mortality in patients with AH. Identification of the key element of SIRS may thus provide a potential therapeutic target.

Keywords: Alcoholic hepatitis, meta-analysis, mortality, systemic inflammatory response syndrome, sepsis

INTRODUCTION

Alcoholic hepatitis (AH) is one of the most fatal conditions in hospitalized patients, frequently leading to multiple organ failure. It is the leading cause of liver-related deaths worldwide, with a 6-month mortality rate of up to 40% (1). Various prognostic models have been developed to stratify the severity of AH and formulate the treatment strategy. Corticosteroid and pentoxifylline are the first-line medications as recommended by the practice guideline (2). Unfortunately, few patients benefit from these pharmacologic treatments. Therefore, alternative treatment modalities are needed. As the pathogenic mechanism that leads to early death is unclear, determining the central element in the mechanism of death could help in establishing new-targeted therapy.

Patients with AH are known to be susceptible to bacterial infection. Sepsis is frequently observed in these patients and is an important mortality predictor (3). However, up to 60% of patients with AH show the features of systemic inflammatory response syndrome (SIRS) in the absence of infection during hospitalization (4,5) secondary from alterations in the hemodynamic circulation and from liver-related complications affecting the changes in the white blood cells and vital signs. This sterile inflammation is a major pathogenic factor in several liver disorders, including nonalcoholic steatohepatitis, drug-induced liver injury, and ischemic liver disease, and appears to be a key determinant for liver fibrosis and carcinogenesis (6). Moreover, SIRS aggravates the severity of encephalopathy and leads to poor outcomes in patients with acute liver failure and

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Received: March 24, 2016 **Accepted:** July 13, 2016

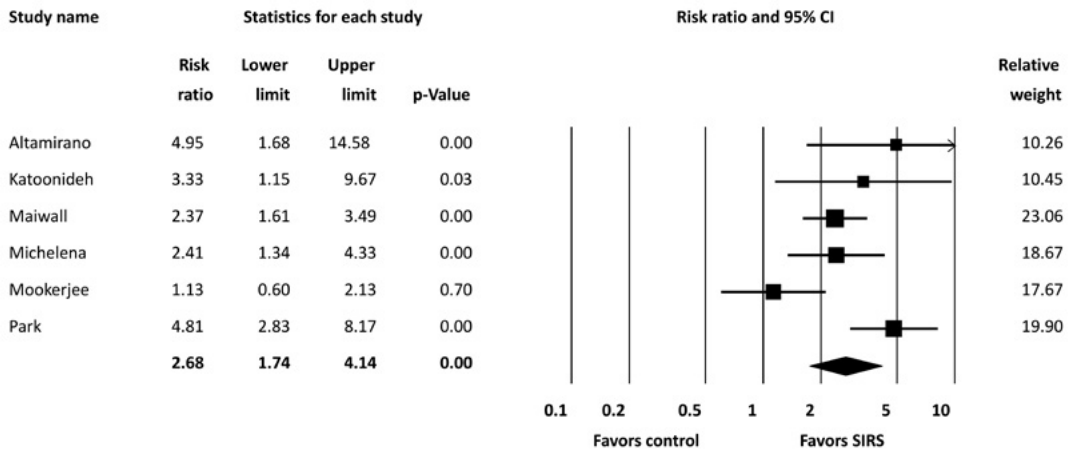

Figure 1. Forest plot of the included studies comparing the risk of mortality in alcoholic hepatitis patients with and without systemic inflammatory response syndrome; a diamond data marker represents the overall RR and 95% CI for the outcome of interest

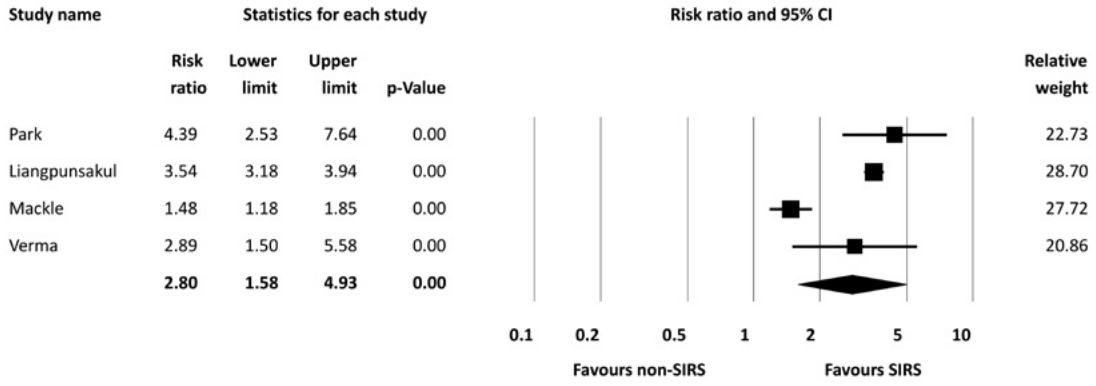

Figure 2. Forest plot of the included studies comparing the risk of mortality in alcoholic hepatitis patients with and without sepsis; a diamond data marker represents the overall RR and 95% CI for the outcome of interest.

increased mortality rates with the greater magnitude of SIRS (7). Another observational study indicated that the presence of SIRS on admission was associated with in-hospital mortality in patients with acute-on-chronic liver failure (8). In cirrhotic patients, SIRS is associated with portal hypertension-related complications, poor hospital outcomes, and mortality. Furthermore, it is closely related to the severity of liver disease as shown by the MELD score (9-11). Interestingly, in patients with severe alcoholic liver disease, SIRS appeared to be an independent predictor for alcohol-related acute chronic liver failure (12).

Recent studies addressing the importance of SIRS in patients with AH have been conducted (5,13,14). Thus, to better characterize the effect of SIRS, we conducted a systematic review and meta-analysis of the observational studies in the literature that compared the risk of mortality in hospitalized patients with AH who had SIRS vs. non-SIRS as our primary outcome and sepsis vs. non-sepsis as our secondary outcome.

MATERIALS AND METHODS

We followed the established guideline for the meta-analysis of observational trials (15). We registered our systematic review and meta-analysis in PROSPERO (registration number: CRD42015029799).

Data sources and search strategy

Two investigators (SU and VJ) searched for the titles of articles in PubMed/MEDLINE and EMBASE. We performed a search from inception to January 2016 and did not restrict the publication date using the search strategy detailed in Figure 3 in the supplementary material. The references of selected articles were also manually searched. No language limitation was applied.

Inclusion criteria

Our inclusion criteria were (1) published observational cohort studies assessing the risk between SIRS or sepsis and mortality in hospitalized patients with AH without other causes of liver diseases, (2) participants aged ≥18 years, (3) risk ratio (RR) or sufficient data to calculate RR were provided, (4) participants without SIRS or without sepsis were used as a reference group. In order to assess the quality of the studies, review articles, case reports, abstracts, and unpublished studies were not included.

Data extraction

Two investigators independently extracted the following data: author, year of publication, study design, study location, participant characteristics, definition of SIRS and sepsis, diagnosis of alcoholic liver disease, confounder adjustments, and quality

Search Strategy:

MEDLINE

1 exp Liver Diseases, Alcoholic/
2 exp Hepatitis, Alcoholic/or hepatitis alcoholic.mp.
3 alcoholic liver disease.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4 1 or 2 or 3
5 exp Systemic Inflammatory Response Syndrome/or sirs.mp.
6 exp Sepsis/or sepsis.mp.
7 exp Shock, Septic/
8 exp Multiple Organ Failure/
9 Septicemia.mp. or exp Sepsis/
10 exp Intensive Care Units/or exp Intensive Care/
11 5 or 6 or 7 or 8 or 9 or 10
12 4 and 11

Embase

((('alcoholic liver disease'/exp or 'alcoholic liver disease') or (alcoholic and hepatitis)) and (('systemic inflammatory response syndrome'/exp or 'systemic inflammatory response syndrome') or sirs or ('sepsis'/exp or 'sepsis') or ('septic shock'/exp or 'septic shock') or ('multiple organ failure'/exp or 'multiple organ failure') or ('septicemia'/exp or 'septicemia') or ('intensive care units'/exp or 'intensive care units') or ('intensive care'/exp or 'intensive care'))) and [embase]/lim not [medline]/lim

Figure 3. Search strategy

assessment. Any conflicting opinions on data extraction were resolved by discussion between the investigators.

Assessment of quality

The quality of each study was assessed with the use of the Newcastle-Ottawa Scale (NOS). Two investigators independently reviewed and assessed the studies in three main areas: (a) selection of the study groups, (b) comparability between the groups, and (c) ascertainment of the exposure of interest for the case–control study and that of the outcome of interest for a cohort and cross-sectional study (16). A total score of ≤3 was considered poor, while 4–6 was considered moderate, and 7–9 was deemed high quality. Poor quality studies were excluded from our analysis.

Exposure and outcome measures

Patients were considered to have SIRS if they fulfilled at least two of the following criteria: body temperature <36°C or >38°C, heart rate >90 beats/min, respiratory rate >20 beats/min, leukocyte count <4,000 or >12,000 cells/μL, or the presence of >10% immature neutrophils (band forms) according to the American College of Chest Physicians Society of Critical Care Medicine consensus definition (17). Sepsis was defined as the presence of infection together with a systemic manifestation of infection. The diagnosis of alcoholic hepatitis was based on the following data: appropriate level of alcohol abuse with clinical, laboratory, radiological and/or histological evidence of liver disease by each study's definition. Mortality was defined as all-cause mortality at 90 days or available data closest to 90 days.

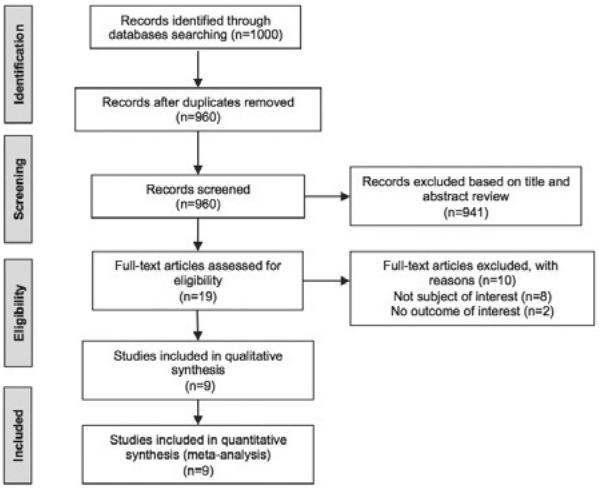

Figure 4. Search methodology and selection process

Statistical analysis

The meta-analysis was conducted using the Comprehensive Meta-Analysis 3.3 software from Biostat, Inc. We calculated a pooled effect estimate of the RR of mortality with 95% confidence intervals (CI) by comparing between a group of SIRS vs. non-SIRS patients as our primary outcome and sepsis vs. non-sepsis patients as our secondary outcome using a random-effects model based on an assumption that the effects being estimated in the different studies were not identical but did follow some distribution. Tests for heterogeneity were performed using chi-square tests with a significant level set at $p<0.10$. A value of I^2 of 0%–25% indicated insignificant heterogeneity, 26%–50% low heterogeneity, 51%–75% moderate heterogeneity, and 76%–100% high heterogeneity (18). We intended to assess publication bias using funnel plot techniques and Egger's regression test as appropriate.

RESULTS

The initial search yielded 960 articles; 941 articles were excluded based on a title and abstract review. A total of 19 articles underwent full-length review. Ten articles were excluded (two articles had no outcome of interest, while eight articles did not relate to a study in the subjects of interest). Data was extracted from six cohort studies (five retrospective cohort studies (5,13,14,19,20) and one prospective cohort study (4)) involving 1,264 patients (507 had SIRS), and four cohort studies (all retrospective cohort studies (3,14,21,22)) involving 57,529 patients (1,449 had sepsis). There were two studies assessing the mortality comparing AH patients with SIRS versus sepsis involving 527 patients (all retrospective cohort studies (5,13)). Figure 4 outlines the search methodology. Table 1 and Table 2 describe the detailed characteristics and quality assessment of the included studies for SIRS and sepsis, respectively.

There were significant associations between SIRS and mortality compared with non-SIRS, with a pooled RR of 2.7 (95% CI 1.74–4.14, $p<0.01$, $I^2=50\%$, $p_{heterogeneity}=0.09$) (Figure 1), and also sepsis and mortality compared with non-sepsis, with a pooled RR of 2.8 (95% CI 1.58–4.93, $p<0.01$, $I^2=94\%$, $p_{heterogeneity}=0.015$) (Figure 2). However, comparing between patients with SIRS and with

sepsis, there was no significant difference among them, with a pooled RR of 0.98 (95% CI 0.75–1.28, I^2=0%, $p_{heterogeneity}$=0.62) (Figure 5). Publication bias was not assessed as there were inadequate numbers of included studies to properly assess funnel plot.

DISCUSSION

In this systematic review and meta-analysis, we demonstrated a significantly higher mortality among AH patients with SIRS compared with non-SIRS controls, with a pooled RR of 2.7, as well as higher mortality in sepsis compared with non-sepsis controls, with a pooled RR of 2.8. The comparison between patients with SIRS and sepsis showed no significant difference in mortality. Our meta-analysis suggests that both SIRS and sepsis appear to be major determinants of mortality in patients with AH.

Several factors may explain these results. First, sepsis in some patients might be difficult to detect during the early period of hospitalization due to the obscure presentations. These patients are prone to have bacterial infection because of poor liver function, immune defects, and prior hospitalization or infection (23,24). Bacterial infection is clearly associated with poor

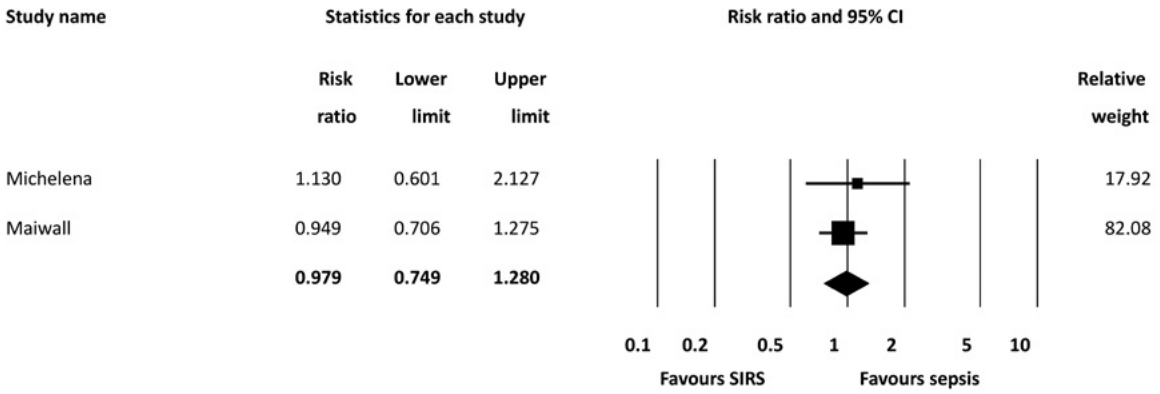

Figure 5. Forest plot of the included studies comparing the risk of mortality in alcoholic hepatitis patients with systemic inflammatory response syndrome and those with sepsis; a diamond data marker represents the overall risk ratio and 95% confidence interval for the outcome of interest

Table 1. Characteristics of the included studies related to systematic inflammatory response syndrome

	Michelena et al. (13)	Maiwall et al. (5)	Altamirano et al. (19)	Mookerjee et al. (20)	Katoonizadeh et al. (4)	Park et al. (14)
Country	Spain	India	Spain	United Kingdom	Belgium	Korea
Year	2015	2015	2012	2011	2010	2015
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort	Retrospective cohort
Timing of SIRS assessment	Within the first 48 hours of admission	On admission	On admission	On admission	Within the first 48 hours of admission	On admission
Diagnosis of AH by biopsy	+	+	+	+	+/–	+/–
Cases	75	236	51	36	34	75
Total number	162	365	103	68	51	515
Mean age (years)	50	45	N/A	51	51	54.4
Female (%)	29	2.5	34.6	24	37	7.2
Timing of mortality assessment (days)	90	90	90	28	In-hospital	30
Confounder adjustment	N/A	MELD, acute kidney injury progression	N/A	N/A	Age, histological presence of marked ductular bilirubinostasis and mallory bodies	Child–Pugh score, MELD, Maddrey's DF score, bacterial infection, WBC, hemoglobin, albumin, creatinine, C-reactive protein, procalcitonin
Quality assessment (Newcastle-Ottawa scale)	Selection: 4 Comparability: 1 Outcome: 3	Selection: 3 Comparability: 1 Outcome: 3	Selection: 3 Comparability: 1 Outcome: 3	Selection: 3 Comparability: 1 Outcome: 3	Selection: 4 Comparability: 1 Outcome: 1	Selection: 3 Comparability: 2 Outcome: 3

AH: alcoholic hepatitis; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; Maddrey's DF: Maddrey's discriminant function; MELD: Model for End Stage Liver Disease; N/A: not applicable; WBC: white blood cell

Table 2. Characteristics of the included studies for sepsis

	Mackle et al. (21)	Park et al. (14)	Verma et al. (22)	Liangpunsakul (3)
Country	United Kingdom	Korea	United States	United States
Year	2006	2015	2006	2011
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort
Timing of sepsis assessment	N/A	On admission	N/A	N/A
Diagnosis of AH by biopsy	N/A	+/–	-	+/-
Cases	42	75	38	1,236
Total number	106	515	99	56,809
Average age (years)	51	54.4	44	53.2
Female (%)	43.9	7.2	N/A	26.8
Timing of mortality assessment (days)	180	30	In-hospital	In-hospital
Confounder adjustment	N/A	Child–Pugh score, MELD, Maddrey's DF score, bacterial infection, WBC, hemoglobin, albumin, creatinine, C-reactive protein, procalcitonin	N/A	Age, sex, sepsis, pneumonia, spontaneous bacterial peritonitis, urinary tract infection, acute kidney injury, ascites, hepatic encephalopathy, coagulopathy, licensed practical nurse, nurse aid, registered nurse
Quality assessment (Newcastle-Ottawa scale)	Selection: 3 Comparability: 0 Outcome: 3	Selection: 3 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 1 Outcome: 1	Selection: 3 Comparability: 1 Outcome: 1

AH: alcoholic hepatitis; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; Maddrey's DF: Maddrey's discriminant function; MELD: Model for End Stage Liver Disease; N/A: not applicable; WBC: white blood cell

outcome in these patients. Second, alcohol intake directly affects the alterations of gut permeability and gut microbiomes, resulting in the translocation of microbial products, especially endotoxin, via the portal circulation to the liver. As a consequence, it activates innate immunity, causing an increased release of proinflammatory cytokines (e.g., tumor necrosis factor-alpha, interleukin-1, interleukin-6), which leads to not only the progression of liver injury but also the systemic involvement resulting in SIRS (25,26). Third, the use of mouse models for alcoholic hepatitis-essentially molecules termed "damage-associated molecular patterns" (DAMPs) released from damaged hepatic cells-can act as a molecular trigger for inflammation, resulting in a wide range of immune responses, including the production of proinflammatory cytokine or the localization of immune cells to the site of injury, subsequently initiating SIRS (6,26). DAMPs are broadly applied to self-molecules that have the ability to activate inflammation; for example, cytochrome *c*, HMGB1, uric acid, and inflammasome (26-28).

In mouse models for alcoholic hepatitis, the inhibition of DAMPs was shown to decrease proinflammatory cytokines, the degree of liver inflammation, and liver steatosis (29,30). The identification of DAMPs and further determination of the effect of pharmacologic DAMPs inhibition might guide future immunotherapeutic intervention in order to limit the inflammatory response and to potentially improve the outcome.

There are some limitations of this meta-analysis worthy of consideration. First, the number of trials included in this meta-analysis is relatively small. Nonetheless, our meta-analyses revealed similar effect on the size of the studies and low to moderate heterogeneity among the trials. Second, most of the included trials were retrospective studies, which were subject to different types of bias, such as selection bias and information bias. Additionally, this is a meta-analysis of observational studies, which could contain potential confounders, including age, sex, comorbidities, and prolonged hospitalization, which might affect the risk of having sepsis. Steroid use is a well-known confounder for sepsis and infection. Unfortunately steroid use was not accounted for by either multivariate or subgroup analyses, so we could not exclude this confounder. Third, between-study heterogeneity is present in this study. Possible sources for this include the differences in study sizes and populations. Fourth, we acknowledge that the comparison should be at best between SIRS and sepsis but we can only include two relevant studies for this comparison. Fifth, we could not assess publication bias due to the limited number of included trials; as a result, a favor toward positive studies may have been present. Moreover, a possible incomplete retrieval of articles may contribute to this bias as we searched through only two databases.

In summary, our meta-analysis demonstrates a significant positive association between both SIRS or sepsis and the risk of mortality in hospitalized patients with AH. SIRS might be the key element of cascade events leading to mortality in patients with AH. Further studies are required to identify the key inflammatory mediators that play a role in SIRS in AH in order to develop targeted therapy.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - V.J.; Design - S.U.; Supervision - S.U.; Data Collection and/or Processing - V.J., A.S.; Analysis and/or Interpretation - S.U., A.S.; Literature Review - V.J.; Writer - V.J.; Critical Review - V.J., S.U., A.S.

Acknowledgements: Authors would like to thank Matthew Roslund for validation of the search.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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