Original Article

Incidence, Mortality and Predictors of Acute Kidney Injury in Patients with Cirrhosis: A Systematic Review and Meta-analysis

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Abstract

Background and Aims: Acute kidney injury (AKI) is common in patients with cirrhosis but the incidence is heterogeneous among studies. We performed a meta-analysis to describe the incidence of AKI and its impact on patient mortality in patients with cirrhosis. We also evaluated the admission variables predicting development of AKI. ***Methods:*** A systematic search of various databases was performed up to November 2018. Meta-analyses were performed using random effects models. ***Results:*** Of 18,474 patients with cirrhosis from 30 selected studies, 5,648 developed AKI, with a pooled incidence of 29% (95% confidence interval [CI]: 28-30%, I^2 of 99%). In-hospital mortality assessed in eight studies was six-fold higher among AKI patients, as compared to those without AKI (odds ratio [OR] 6.72, 95% CI: 3.47-13, $p<0.0001$, I^2 of 70%). Three studies on patients admitted to intensive care showed about six-fold higher mortality among AKI patients (OR 5.90, 95% CI: 3.21-10.85, $p>0.0001$). Mortality remained significantly high, at days 30 and 90 and even at 1-year follow up after development of AKI. Of 12 admission variables analyzed, model for end-stage liver disease score, Child-Pugh-Turcotte stage C, presence of ascites, and presence of sepsis/septic shock were statistically significant risk factors for AKI. ***Conclusions:*** AKI occurred in about 29% of patients with cirrhosis and is associated with a six-fold increased risk of in-hospital mortality. Mortality remained high even in long-term follow-up of 1 year. Patients at risk for AKI development can be recognized at admission. Prospective studies are needed to develop strategies for improving outcome of these patients.

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Introduction

Acute kidney injury (AKI) is a common event in the natural history of patients with cirrhosis, with an incidence rate varying from 14% to 50%.[1–3] Furthermore, the diagnosis of AKI in patients with cirrhosis is confounded by fluid overload,[4] the effect of bilirubin on the creatinine assays, and reduced muscle mass in patients with cirrhosis.[5] Splanchnic pooling from portal hypertension in cirrhosis results in decreased effective circulating blood volume and renal blood flow, putting patients at risk for AKI and hepato-renal syndrome.[6]

The definition of AKI has changed over the last two decades, recognizing that an elevation in serum creatinine of ≥0.3 mg/dL from baseline negatively impacts survival. Many definitions have been introduced to define and stage AKI, such as the Risk Injury and Failure (commonly referred to as RIFLE),[7] AKI Network (commonly referred to as AKIN) criteria,[8] and Kidney Disease Improving Global Outcomes (commonly referred to as KDIGO).[9] Variations in the definitions of AKI are one of the most important factors resulting in heterogeneity in the reported incidence of AKI among patients with cirrhosis. That being said, the essence of all the definitions of AKI seem to be similar. Although many studies have examined the incidence and impact on outcomes of AKI in patients with cirrhosis, pooled data from these studies is scarce. We performed this meta-analysis to pool the data from observational studies to define the incidence and etiology of AKI in patients with cirrhosis and its impact on patient survival. We also aimed to examine variables at baseline that could identify patients with cirrhosis who are at risk of developing AKI.

Methods

Study selection criteria

The studies considered in this meta-analysis were case-control or prospective cohort studies of patients with cirrhosis, reporting on the incidence of AKI or/and comparing mortality among patients with versus those without AKI.

Keywords: Acute kidney injury; Cirrhosis; Mortality; Outcomes.

Abbreviations: AKI, acute kidney injury; AKIN, AKI Acute Kidney Injury Network; CI, confidence interval; KDIGO, Kidney Disease Improving Global Outcomes; LFK, Luis Furuya-Kanamori; OR, odds ratio; RIFLE, risk injury and failure.

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Studies reporting mortality at short to medium term (in-hospital, 30 days, and 90 days) or long-term (1 year) were included. Studies were excluded if they did not include incidence and/or mortality associated with AKI in cirrhotic patients or if there were insufficient data for analysis. Studies published only in English language and as full manuscripts were included in the analysis.

Data sources and search strategy

All procedures used in this meta-analysis were consistent with the PRISMA criteria for observational studies.[10] We conducted a comprehensive search of Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Web of Science and Scopus, from January 1990 to November 2018. The search strategy was designed and conducted by experienced library staff. MeSH terms used in the search were 'acute kidney injury' or 'AKI' AND 'cirrhosis' AND 'risk factors' or 'incidence' or 'mortality'.

Two authors (R.T. and Y.H.) independently reviewed the titles and abstracts of the searched literature to identify potential studies for analysis. The full texts of these studies were reviewed for final selection to be included in the meta-analysis. The reference lists of articles with information on the topic were also reviewed for additional pertinent studies. Any discrepancy between these two investigators was resolved by joint re-evaluation of the article in question and consensus among the authors. A flow diagram of included studies is shown in Fig. 1.

The Newcastle-Ottawa scale was used independently by two investigators (R.T. and H.S.) to assess the quality of each selected study for the analysis. In this scale, observational studies were scored across three categories using the following parameters: selection (four questions), comparability (two questions), and ascertainment of the outcome of interest (three questions). For each question, 1 point was given if the study met the criterion, except for comparability of study groups, in which 2 points were awarded if the study controlled for age, sex, or both, and other confounding factors (Supplementary Table 1). Studies with a cumulative score of 7 or more were considered high quality and those with score of ≤6 were considered of low quality. Any discrepancies were addressed by a joint re-evaluation of the article in question and consensus amongst the authors.

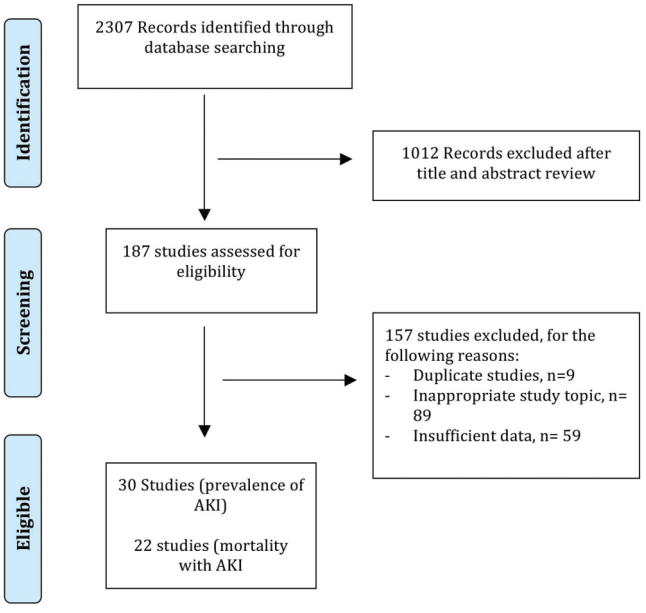

Fig. 1. Search strategy for included studies.

Outcomes

Our primary analysis focuses on the incidence and mortality associated with AKI in patients with cirrhosis. The secondary outcome was to evaluate the risk factors that predicted mortality in these patients

Data abstraction

Data were independently abstracted to a predetermined data collection Microsoft Excel spreadsheet by three investigators (R.T., Y.H and K.C.). For each study, data were collected for study design, location, year of publication, definition of AKI used, patient demographics, follow-up period, and outcomes. Conflicts on data abstraction were resolved by consensus amongst authors and referring to the original article.

Statistical analyses

The random-effects model described by DerSimonian and Laird[11] was used to calculate weighted incidence rate of AKI with corresponding 95% confidence interval (CI). Data were weighted based on sample size in each study. For mortality analysis at various time points, odds ratio (OR) with 95% CI were derived on the odds of dying among AKI patients compared to those without AKI. To identify variables at baseline predictive of AKI risk, ORs were determined for categorical variables and mean difference for continuous variables.

We assessed heterogeneity within groups with the I^2 statistic, which estimates the proportion of total variation across studies. I^2 value >50% suggested heterogeneity of the pooled data.[12] To address heterogeneity, subgroup analyses were performed on studies defining AKI using the AKIN criteria, high quality studies, and prospective studies. Publication bias was assessed by visual inspection of funnel plots and numerically using the Luis Furuya-Kanamori (LFK) estimate on a Doi plot. The scoring was: no asymmetry when the LFK index was within ±1; minor asymmetry when the LFK index exceeded ±1 but was within ±2; major asymmetry when the LFK index exceeded ±2. Publication bias was considered if the given analyses had major asymmetry on the inspection of funnel plots. If publication bias was found on funnel plot, we used the trim and fill for adjusting publication bias.[12,13] All p values were 2-tailed and considered statistically significant if <0.05. Review Manager (version 5.3; Cochrane Inc.) and MetaXL, version 5.1 (EpiGear International Pty Ltd) statistical software program were used to analyze the pooled data (www.epigear.com).

Results

Baseline characteristics of included studies

On the initial literature search, 2307 potentially relevant studies were identified. After screening titles and abstracts, 187 full-text articles were reviewed for study selection. Of

Table 1. Baseline characteristics of included studies

First author, year	Study type	Location of study	Total, *n*	With AKI, *n*	Mean age	% Males	Follow-up period	Definition of AKI
Angeli, 2014	P	Spain	510	98	55	64.9	90 days	AKIN
Bıyık, 2016	RT	Turkey	277	108	62.1	57.8	4 years	KDIGO criteria
Bucsics, 2015	RT	Austria	239	78	54.9	66.9	n/a	AKIN
Chen, 2011	RT	Taiwan	2,375	636	60.73	69.1	58 months	eGFR <60
Choi, 2014	RT	Korea	643	83	57.4	74.3		AKIN
Cholongitas, 2009	P	UK	312	128	49.3	NA	96 weeks	Serum creatinine ≥300 mmol/L
Cholongitas,2009b	RT	UK	412	205	49.3	59.2	17 years	RIFLE
de Araujo, 2014	RT	Brazil	46	20	56.94	63	13months	AKIN
du Cheyron, 2005	RT	France	186	73	56.4	69	5 years	ADQI definition
Fagundes, 2013	P	Spain	375	177	61	62	25 months	AKIN
Hampel, 2001	RT	New Mexico	93	23	57.5	NA	7 years	↑serum creatinine >1.0 mg/dl
Hseih, 2017	RT	Taiwan	117	46	61	72	6 weeks	ICA
Huelin, 2017	P	Spain and Italy	547	290	61	67	90 days	ICA
Hung, 2012	RT	Taiwan	2592	145	57.5	70.8	1 year	ICD-9-CM
Jaques, 2018	P	Switzerland	105	55	58.0	71.4	2 years	AKIN
Jindal, 2015	RT	India	241	55	46.12	85.47	33 months	Mild or moderate AKI with cut-off creatinine at 3 mg/dL
Maiwall, 2015	P	India	451	122	46	86	1 year	AKIN
Marciano, 2017	RT	Argentina	108	37	61.5	59.6	3 years	KDIGO
Nuthalapati, 2017	RT	USA	339	96	57.0	63	5 years	AKIN
Pan, 2016	P	Taiwan	242	152	58	75.7	2 years	AKIN and RIFLE
Piano, 2013	P	Italy	233	61	65.3	64.4	NA	AKIN & conventional criteria
Prakash, 2011	P	India	404	99	48.5	79	16 months	AKIN
Scott, 2013	P	UK	162	110	56.8	65.4	18 months	AKIN
Shi, 2016	RT	China	1167	308	NA	NA	1 year	KDIGO
Tandon, 2016	RT	Canada	4733	1850	60.4	64.3	10 years	KDIGO
Tsien, 2013	P	Canada	90	49	55.8	71.1	2 years	n/a
Warner, 2011	RT	USA	152	107	53	76%	2 years	AKIN
Wong, 2013	P	USA	337	166	55.91	56	30 days	ADQI definition
Wong, 2017	P	Multiple centers in North America	653	307	56.7	64	30 days	ICA
Zhou, 2017	RT	China	333	60	55.68	63.06	2 years	KDIGO
Summary			18,474	5,648	56.8	66.9	Median: 12 months	NA

Abbreviations: ADQI, Acute Dialysis Quality Initiative; AKI, acute kidney injury; AKIN, AKI Network; ICA, International Club of Ascites; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk Injury and Failure; P, prospective; RT, retrospective.

these, 30 studies[14–43] met eligibility criteria and were included for analysis and the remaining 157 were excluded for different reasons (Fig. 1). Of the 30 studies (12 prospective and 18 retrospective) analyzed and including 18,474 patients with cirrhosis (median age 57 years and 67% males), 16 were from the Western world (10 from Europe and 6 from USA or Canada) and the remaining studies were from Asia (*n*=10), Middle East (*n*=1), or South America (*n*=3)

(Table 1). The median Newcastle-Ottawa quality score for the included studies was 8 (range: 6-9) (Supplementary Table 1). A total of 17 studies were high quality and 13 were low quality. Other details and a summary of the included studies are described in Supplementary Table 2. The percentage of patients with baseline kidney dysfunction was not discussed in most studies, as shown in Supplementary Table 3; although, a majority of the studies included patients with some degree of baseline renal dysfunction.

Incidence of AKI

Of the 18,474 patients with cirrhosis in the 30 selected studies, 5,648 had developed AKI, with a pooled incidence of 29% (95% CI: 28-30%). AKI was defined based on the AKIN in 11 studies and the definition of AKI was variable in the remaining studies (Table 1). The pooled data had significant heterogeneity, with an I^2 of 99% and $p<0.0001$ (Fig. 2). No publication bias was seen on visual inspection of forest plot, with minor asymmetry on Doi plot (LFK=1.45) (Supplementary Fig. 1). Heterogeneity remained high when pooled incidence was analyzed only for prospective studies (40%, 95% CI: 38-41%), for studies that used AKIN criteria (29%, 95% CI: 28-31%), and for studies with high quality (40%, 95% CI: 39-41%) (Supplementary Fig. 2A, 1B and 1C, respectively). One study was performed before 2005 and in order to ensure the universal definitions of AKI after 2005, subgroup analysis was performed after the exclusion of that study, which revealed the same incidence of AKI (29%, 95% CI: 28-30%) after exclusion of the above mentioned study.[26]

Mortality risk: comparing patients with AKI vs. no AKI

Of the 30 studies included, 22 reported patient mortality data for a median follow-up of 12 months (range: 30 days to 10 years) (Table 1). In-hospital mortality was assessed in eight studies. The rate of mortality among AKI patients was 215/620 (34.6%) vs. 61/624 (9.7%), which was six-fold higher among AKI patients compared to those without AKI (OR [95% CI]: 6.72 [3.47-13], $p<0.0001$). Separate analysis from three studies on patients admitted to intensive care also showed about six-fold mortality among AKI patients (277/353 (78%) vs. 154/387 (39.7%); OR [95% CI]: 5.90 [3.21-10.85], $p>0.0001$). Mortality at 30 days reported in seven studies was over three-fold higher with AKI (422/995 (42.4%) vs. no AKI 841/3973 (21.1%), OR [95% CI]: 3.37 [2.35-4.84], $p>0.0001$). Similarly, mortality remained higher at 90 days and at 1-year follow-up for those with compared to those without AKI (47.1% vs. 16.4%, OR [95% CI]: 4.43 [2.93-6.70], $p>0.00001$) and (68.3% vs. 45.1%, OR [95% CI]: 5.37 [2.45-11.79], $p>0.00001$). However, there was significant heterogeneity for all the analyses (Fig. 3 A-E). No publication bias was seen on visual inspection of forest plots (Supplementary Fig. 3 A-E).

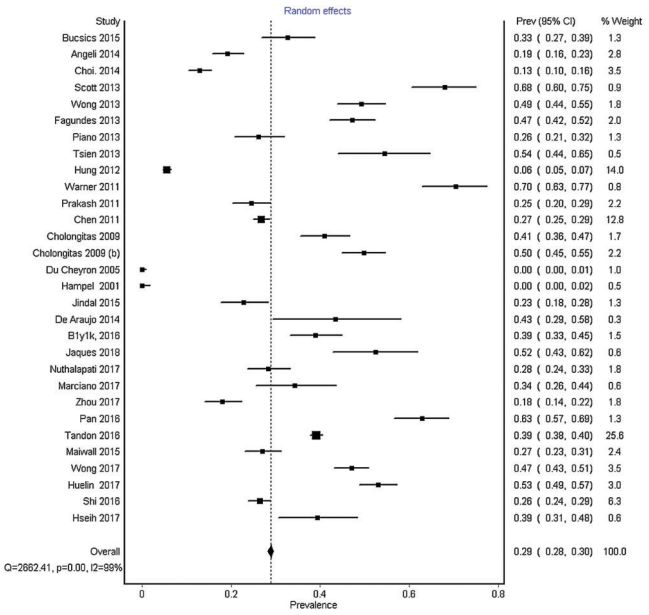

Fig. 2. Forest plot depicting pooled incidence of acute kidney injury in patients with cirrhosis.

Risk factors associated with development of AKI

A total of 12 variables at admission were analyzed among 22 studies as predictors for the development of AKI. Of these, four predicted the risk of AKI, given as OR (95% CI): model for end-stage liver disease score, 5.89 (5.17-6.62); Child-Pugh-Turcotte stage C, 2.51 (1.83-3.44); presence of ascites, 2.06 (1.25-3.41); and presence of sepsis/septic shock, 2.72 (1.05-7.06) (Fig. 4 A-D). Interestingly, history of variceal bleed was associated with a decreased risk of AKI, 0.69 (0.48-0.99) (Fig. 4E). Other factors, including etiology of cirrhosis (alcoholic and viral), encephalopathy, bacterial infection on admission, male sex, age, and diabetes mellitus were not associated with risk of AKI (Supplementary Fig. 3A-G).

Discussion

The main findings of this meta-analysis on pooled data from 30 studies of patients with cirrhosis are a high incidence of AKI (at 29%) and higher mortality during hospitalization and on follow-up to 1 year among patients who develop AKI when compared to those who do not. Further, patients at risk of development of AKI can be identified at presentation or hospitalization with higher model for end-stage liver disease or Child-Pugh-Turcotte score with ascites and/or sepsis/shock.

Portal hypertension with resultant splanchnic pooling of blood in patients with cirrhosis results in decreased effective circulating blood volume, setting the stage for development of AKI with decompensation of cirrhosis or introduction of any precipitant, such as volume loss, use of diuretics, administration of radio-contrast agents or nephrotoxic drugs, and onset of infections or sepsis.[44] Cirrhosis is the 12th leading cause of mortality in the general population, with over 40,000 annual deaths from this disease.[45] In one study, mortality rate among patients with cirrhosis was over 20% at 2 years.[46] Not only does AKI portend a worse prognosis in these patients but the mortality risk remains elevated in these patients at 1-year follow-up among those surviving the index hospitalization or development of event. Data in the current literature regarding renal recovery and its effect on mortality is scant, but a recent study shows a high mortality rate (of 15%) in cirrhosis patients who experienced complete renal recovery after an AKI episode, as observed in the current analysis.[15] Clearly, AKI represents a significant event in the natural course of these patients with cirrhosis, and this may be viewed as a sixth stage in the already five-stage

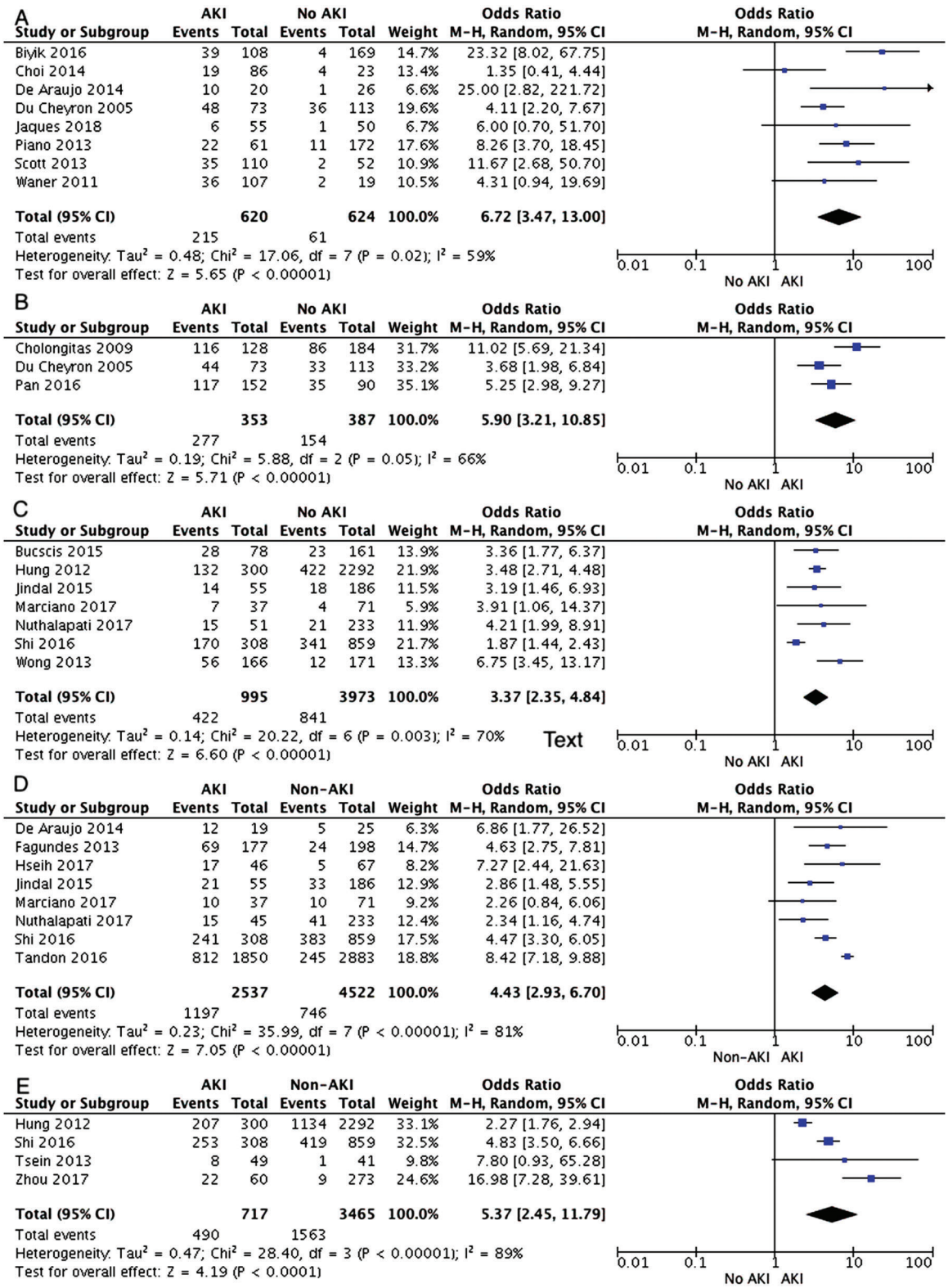

Fig. 3. Forest plots on mortality outcomes comparing cirrhosis patients with acute kidney injury vs. without acute kidney injury for A) overall in-hospital mortality, B) in-hospital mortality for intensive care patients, C) mortality at 30 days follow-up, D) mortality at 90 days follow-up, E) mortality at 1-year follow-up.

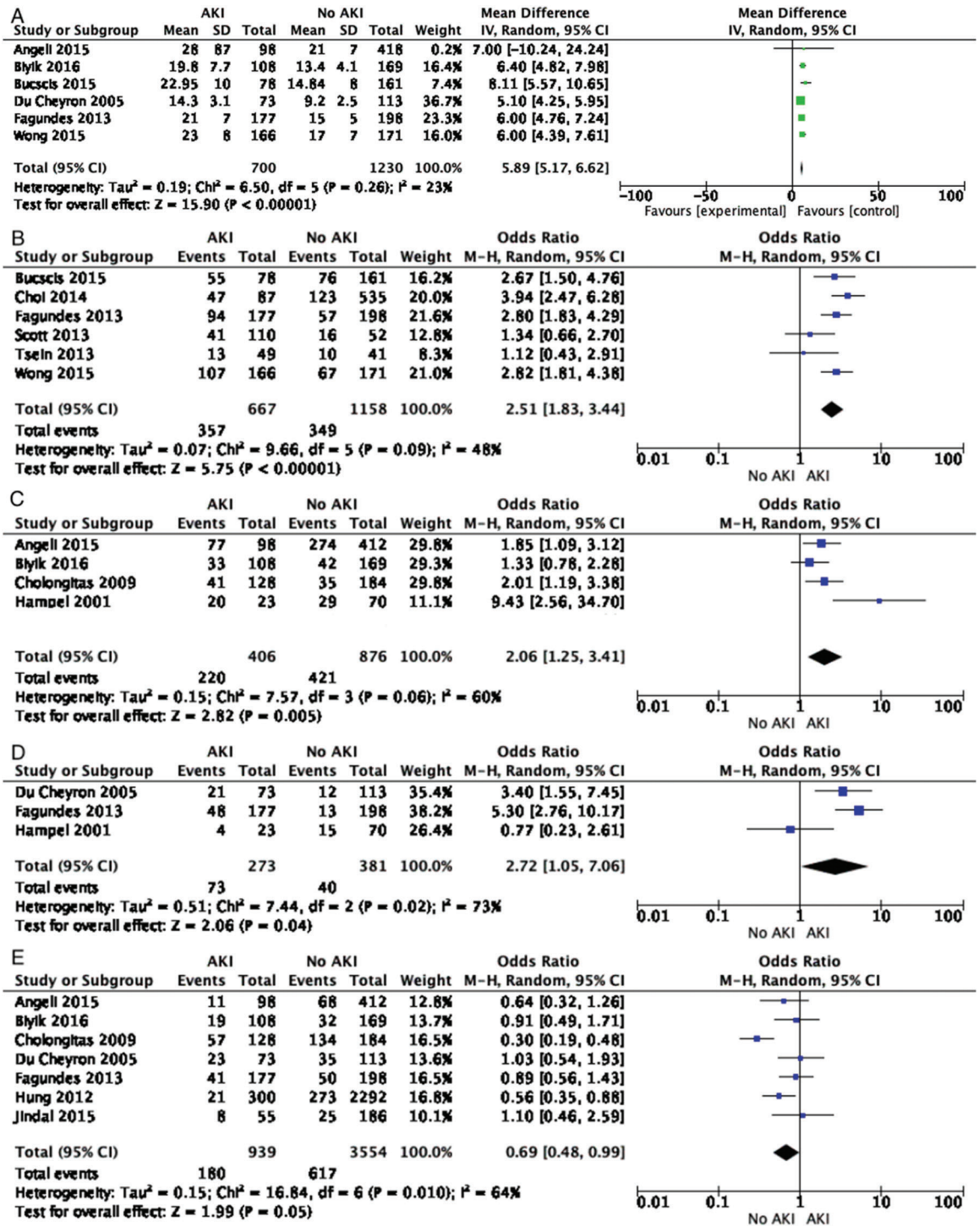

Fig. 4. Forest plots showing admission variables predicting acute kidney injury.

A) Model for end-stage liver disease score, B) Child-Pugh-Turcotte score, C) presence of ascites, and D) presence of sepsis/septic shock. Risk of acute kidney injury is reduced among patients with variceal bleeding (E).

model of cirrhosis, with linear increase in short-term and long-term mortality.[47] It has been shown in prospective studies that the index episode of AKI is a risk factor for subsequent episodes of AKI.[48] With each episode of AKI, the renal reserve declines due to the inability of kidneys to recover function completely to original baseline level and resulting in risk for development of chronic kidney disease and impacting the outcomes negatively.[31,33]

While patients with cirrhosis constitute a heterogeneous cohort, the subpopulations at an increased risk of developing AKI have not been sufficiently studied. In our pooled analysis, model for end-stage liver disease score, Child-Pugh stage, presence of ascites, and presence of severe sepsis/septic shock were associated with an elevated risk of developing an AKI. Severe sepsis/septic shock has been studied as independent risk factors for developing AKI regardless of cirrhosis. Also, association of AKI with model for end-stage liver disease score and Child-Pugh class found in our study are in line with the prior studies.[48–50] Model for end-stage liver disease score is the most frequently used score all over the world to estimate patient outcomes and survival among patients with cirrhosis. Renal function apart from serum bilirubin and coagulation status is an important component of the model for end-stage liver disease score. Use of diuretics, large volume paracenteses, and fear of physicians to give volume expansion are some speculated reasons explaining higher risk of AKI in patients with ascites.[51] Interestingly, presence of a history of or current admission with a variceal bleed was associated with a decreased risk of AKI. Patients with variceal bleeding receive antibiotics for spontaneous bacterial peritonitis prophylaxis, as recommended by guidelines from major societies; this use of spontaneous bacterial peritonitis prophylaxis may be the reason for lower incidence of AKI in this cohort.[52] Diabetes and the etiology of cirrhosis were not found to be associated with AKI.

Pooled data on a large patient population with cirrhosis is the strength of this meta-analysis. Furthermore, our study also identified the predictors of AKI apart from pooled incidence and risk of mortality. However, our study does have some limitations. Studies included in our meta-analysis varied on study design, patient population, and status of cirrhosis, resulting in significant heterogeneity. Pooled data using the individual patient data from these studies may potentially overcome this limitation and provide more homogeneous data on incidence, impact on outcomes, and variables predictive of AKI. Furthermore, due to the very limited data available in the included studies regarding the mortality rates among subgroups with different stages of AKI, we could not perform a pooled mortality analysis based on severity of AKI. To explore the heterogeneity, meta-regression was considered with various predictor variables including sex, viral cirrhosis, alcoholic cirrhosis, Child-Pugh score, concomitant diabetes, presence of ascites, variceal bleeding, encephalopathy, bacterial infection, septic shock/sepsis, mean difference in age and model for end-stage liver disease scores. The number of studies in each individual analysis was limited (all <10). Moreover, information for each predictor variable was also poorly present. At most, one predictor (sex) was present for three studies in one outcome (30-day mortality); the rest were present for one or two studies only. Hence, meta-regression was not performed based on poor information availability of predictor-variables.[53]

In conclusion, AKI is common in cirrhotic patients, and leads to increased mortality among patients admitted to hospital in the wards as well as in the ICU, which remained high even at long-term follow-up at 1 year. Multicenter prospective studies are also suggested using pre-defined criteria to define AKI, study outcomes, and risk factor variables as basis for development of homogeneous data.

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None to declare.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contributed to concept, data interpretation drafting and revision of manuscript (RT, AKS), data collection, drafting and revision of manuscript (YH), data collection and interpretation (KS), and data collection (SR, HS).

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