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Homocysteine and the Mortality of Critically Ill Patients: A Meta-Analysis

Authors
Fawei Yuan[1,2], Kun Zheng[1,2]

Affiliations
1 Department of Intensive Care Unit, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Edong Healthcare Group, Huangshi, China
2 Hubei Key Laboratory of Kidney Disease Pathogenesis and Intervention, Huangshi, Hubei, China

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Correspondence
Dr. Kun Zheng
Huangshi Central Hospital
Intensive Care Unit
No. 141 Tianjin Road
435000 Huangshi
China
Tel.: 86-714-3189999
kunzheng_9322@163.com

ABSTRACT

Prevalence of hyperhomocysteinemia (HHcy) is high in critically ill patients. However, the association between serum homocysteine level and outcomes of the critically ill patients remains unknown. We performed a meta-analysis of cohort studies to comprehensively evaluate the above association. Relevant cohort studies were identified by search of electronic databases including PubMed, Embase, Web of Science, Wanfang, and CNKI from the inception of the databases to February 5, 2022. A randomized-effect model incorporating the possible between-study heterogeneity was used to pool the results. Overall, 16 cohorts with 1663 critically ill patients who were admitted to the intensive care unit (ICU) were involved in the meta-analysis. Pooled results showed that compared to non-survivors of the critical illnesses, survivors had significantly lower serum level of Hcy at ICU admission [mean difference (MD): −3.42 µmol/l, 95 % confidence interval (CI): −5.89 to 0.94, p = 0.007; I2 = 86 %]. Subgroup analysis showed that the difference of Hcy between survivors and non-survivors was significant in Asian patients (MD: −8.17 µmol/l, p < 0.001), but not in non-Asians (MD: 0.30 µmol/l, p = 0.62; p for subgroup difference < 0.001). Moreover, meta-analysis with seven cohorts, all including Chinese patients, showed that HHcy at ICU admission was independently associated with a higher risk of all-cause mortality in critically ill patients (odds ratio: 2.99, 95 % CI: 2.26 to 3.97, p < 0.001; I2 = 69 %). A higher serum level of Hcy at ICU admission may be associated with an increased risk of all-cause mortality in critically ill patients, particularly in the Chinese population.

Introduction

Hyperhomocysteinemia (HHcy) is a common metabolic disorder characterized by increased serum level of homocysteine (Hcy), an intermediate product of the methionine cycle [1–3]. Pathophysiologically, HHcy has been related with activated oxidative stress, excessive endoplasmic reticulum stress, altered DNA methylation, endothelial dysfunction, and activated immuno-inflammatory response, all of which are involved in the pathogenesis and progression of atherosclerosis and vascular injuries [4–6]. The prevalence of HHcy in general population may be different according to the diagnostic criteria of HHcy and the region of the studies. In the Framingham study population, the prevalence of HHcy was 29.3 % using the diagnostic criteria of Hcy > 14 µmol/l [7]. In China, using the diagnostic criteria of Hcy > 15 µmol/l, a recent updated meta-analysis including 338 660 participants showed that the overall prevalence of HHcy was 37.2 %, which was gradually increased over time [8]. Clinically, HHcy has been related to increased risks of cardiovascular diseases [9], stroke [10], cognitive decline, and dementia [11]. Moreover, HHcy has been suggested as a risk factor of death in general population [12]. Interestingly, accumulating evidence suggests that the prevalence of HHcy is also high in patients of acute clinical conditions, such as the critically ill patients who are admitted to the intensive care unit (ICU) [13]. Besides, higher Hcy has also been detected in patients with acute diseases as compared to healthy controls, such

as patients with the acute phase of atherothrombotic stroke [14] and patients with acute pancreatitis [15], and the acute increment of Hcy in these patients may be related to pathophysiological changes including endothelial dysfunction [16]. However, the potential prognostic significance of serum Hcy on clinical outcomes of patients with critical illnesses remains unclear. Some early studies failed to show that the serum level of Hcy was different between survivors and non-survivors of the critically ill patients [17–21], while other studies showed that HHcy at baseline may be a risk factor of increased mortality in these patients [22–26]. Therefore, we performed a systematic review and meta-analysis to comprehensively evaluate the potential association between serum Hcy and outcomes of the critically ill patients.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [27, 28] guideline and Cochrane's Handbook for Systematic Review and Meta-Analysis [29] were followed in this study.

Literature search

Studies were conducted by search of Medline, Web of Science, and Embase using strategy based on the combined key words: (1) "homocysteine" OR "Hcy" OR "hyperhomocysteinemia"; (2) "intensive care" OR "ICU" OR "critically ill" OR "critical illness" OR "trauma" OR "APACHE" OR "sepsis" OR "acute respiratory distress" OR "multiple organ system failure" OR "mechanical ventilation", from inception of the database to February 5, 2022. Only studies with human subjects were included. No restriction was applied regarding the language of publication. We also screened the citation lists of the related original and review papers in a manual manner as a complementation.

Inclusion and exclusion criteria for the potential studies

The objective of the study was to determine the association between serum Hcy at ICU admission and all-cause mortality of the critical ill patients. Accordingly, the possible difference of serum Hcy was firstly determined between survivors and non-survivors, and then, the association between HHcy and all-cause mortality in the critical ill patients was evaluated. The following inclusion criteria were applied: (1) designed as cohort studies; (2) included patients with critical illnesses who were admitted to ICU; (3) serum level of Hcy was measured at ICU admission and analyzed as exposure; (4) patients were followed for the outcome of all-cause mortality; and (5) reported the serum Hcy at admission in survivors and non-survivors, and/or the relative risk of all-cause mortality between patients with and without HHcy at ICU admission. Diagnosis of HHcy was in accordance with the criteria used among the original studies. Reviews, cross-sectional studies, studies that did not include patients with critical illnesses admitted to ICU, studies that did not measure serum Hcy, or studies that did not report all-cause mortality were excluded.

Data collection and quality evaluation of the included studies

Two independent authors conducted database search, data collection, and assessment of study quality separately. In case of disagreement, it was resolved by discussion and consensus between the two authors. The data collected were: (1) general study information and study design; (2) patient characteristics, including the diagnosis, age, and sex; (3) timing of serum Hcy measurement and analytic methods; (4) follow-up duration and number of patients who died during follow-up; and (5) outcomes reported and variables controlled for studies that reported the relative risk of all-cause mortality between patients with and without HHcy. The Newcastle-Ottawa Scale (NOS) [30] was used for assessing the quality of the studies. Studies were graded according to selection of study groups, comparability of groups, and ascertainment of exposure and outcomes. A maximum of nine stars represents the lowest risk of bias.

Statistical methods

The difference of serum Hcy between the survivors and non-survivors of critically ill patients was measured with mean difference (MD) and its 95 % confidence interval (CI). In addition, the association between HHcy at ICU admission and all-cause mortality of the critically ill patients was presented as odds ratio (OR) and its 95 % CI. Logarithmical transformation of OR data and stand error (SE) extracted from each study were performed to achieve normalized distribution [31]. To evaluate the extent of between-study heterogeneity, the Cochrane's Q-test was performed and the I^2 statistic was estimated as previously described [31, 32]. An $I^2 > 50\,\%$ reflected significant heterogeneity. A random-effect model was applied to pool the results after incorporating of possible between-study heterogeneity [29]. Sensitivity analyses by excluding one cohort at a time were performed to evaluate the stability of the results. If at least ten datasets were available for the outcome, subgroup analyses were performed to evaluate the possible influences of study characteristics on the outcome, such as ethnicity of the patients, study design, types of ICU admitted (medical, surgical, or mixed), follow-up durations, and quality scores. Medians of continuous variables were used to define subgroups. Funnel plots were constructed and visual inspection of their symmetry was performed to assume the possible existence of publication bias [33]. Egger's regression test [33] was also performed to test possible publication bias. We used RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata (Version 17.0; StataCorp LLC, Texas, USA) software for the statistical analyses and a $p < 0.05$ suggests statistical significance.

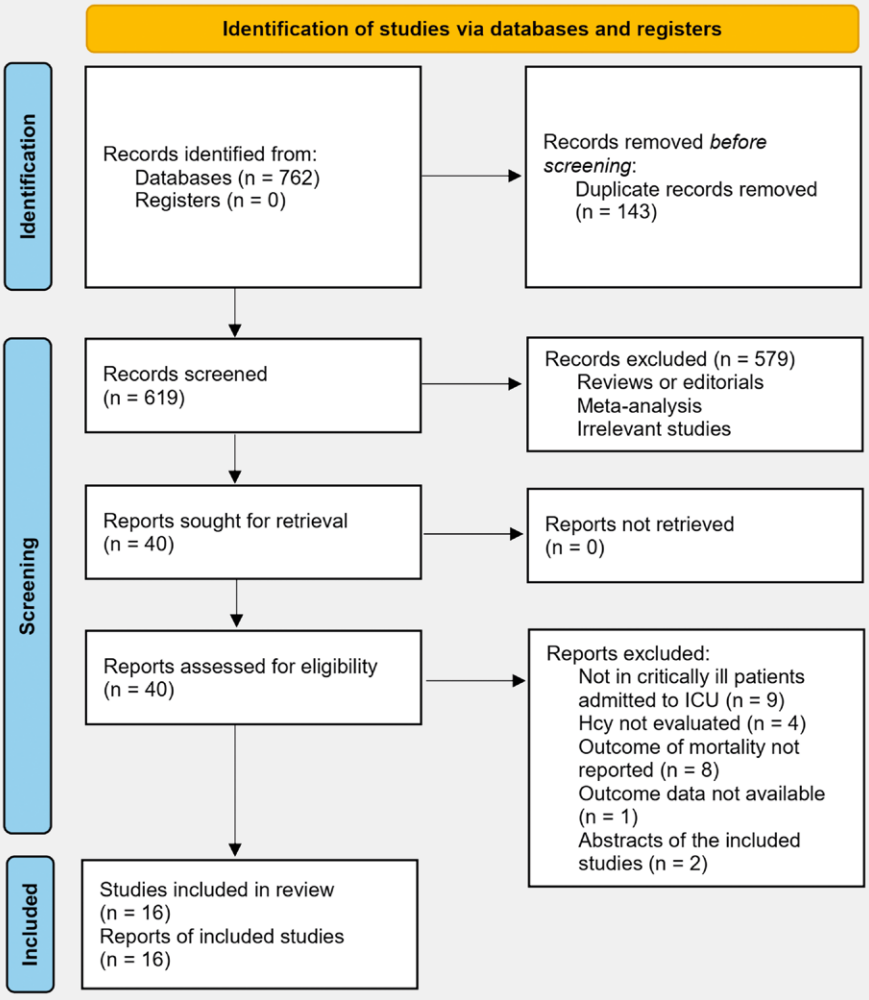
Results

Study identification

As shown in ▶ **Fig. 1**, 619 articles were retrieved after search of electronic databases after removing duplications. Subsequently, 579 were further excluded due to the lack of relevance. The remaining 40 studies were screened with full text, and 24 were further removed for the reasons in ▶ **Fig. 1**. Finally, 16 cohort studies [17–26, 34–39] were available for the meta-analysis.

Characteristics of the included studies

As shown in ▶ **Table 1**, 16 cohort studies were included in the meta-analysis. Six of them were prospective cohort studies



▶ **Fig. 1** Flow diagram of the database search and study identification.

[17, 19, 21, 34, 36, 39] and the remaining were retrospective cohort studies [18, 20, 22–26, 35, 37, 38]. These studies were performed in Austria [17, 18, 20], Greece [21], Brazil [19], the United States [35, 36], Iran [34], and China [22–26, 37–39], and all included critically ill patients who were admitted to the ICU, such as patients with sepsis, pulmonary embolism, acute myocardial infarction, severe acute pancreatitis, respiratory failure, intracerebral hemorrhage, and severe multiple trauma etc.. Serum Hcy was measured within 48 hours of ICU admission, and the follow-up durations varied from 2 weeks to 12 months. Overall, 375 patients died during follow-up. Difference of serum Hcy at ICU admission between survivors and non-survivors was reported in 13 studies [17–21, 24–26, 34–37, 39] with 985 patients, while the association between HHcy and all-cause mortality of the critically ill patients was reported in 7 studies [22–26, 37, 38] with 1013 patients. For the latter studies, HHcy was all defined as serum Hcy > 15 µmol/l, and the association between HHcy and all-cause mortality was analyzed with multivariate models incorporating age, sex, and other parameters of disease severity. The NOS of the included studies were five to eight stars, suggesting moderate to good quality (▶ **Table 2**).

Difference of serum Hcy between survivors and non-survivors

Overall, 13 studies [17–21, 24–26, 34–37, 39] with 985 critically ill patients evaluated the possible difference of Hcy at ICU admission between the survivors and non-survivors. Pooled results showed that compared to the non-survivors, survivors had a significantly lower serum level of Hcy at ICU admission (MD: –3.42 µmol/l, 95 % CI: –5.89 to –0.94, p = 0.007; I^2 = 86 %; ▶ **Fig. 2a**). Sensitivity analyses by excluding one cohort at a time showed similar results (MD: –2.64 to –4.00 µmol/l, p all < 0.05). Subgroup analysis showed that the difference of Hcy between survivors and non-survivors was significant in Asian patients (MD: –8.17 µmol/l, p < 0.001), but not in non-Asians (MD: 0.30 µmol/l, p = 0.62; p for subgroup difference < 0.001; ▶ **Fig. 2b**). Further subgroup analyses showed consistent results in prospective and retrospective cohort studies, and in patients admitted to medical and surgical ICU (p for subgroup dif-

▶ **Table 1** Characteristics of the included cohort studies.

Study [Ref]	Country	Design	Patient characteristics	Sample size	Mean age (years)	Men (%)	Timing of Hcy measuring	Cutoff for Hcy	Follow-up duration	Patients died	Outcomes reported	Variables adjusted
Schindler 2000 [17]	Austria	PC	Medical or surgical patients with critical illnesses	55	60.3	71.4	Within 24 h after ICU admission	NA	1 month	15	Difference of Hcy	None
Stoiser 2000 [18]	Austria	RC	Patients with sepsis	14	63	50	24 h after ICU admission	NA	1 month	7	Difference of Hcy	None
Tsantes 2010 [21]	Greece	PC	MV patients with severe sepsis or septic shock	102	61.9	66.7	At ICU admission	NA	3 months	57	Difference of Hcy	None
Ploder 2010 [20]	Austria	RC	Patients with sepsis	18	44.2	77.8	Within 24 h after ICU admission	NA	2 weeks	7	Difference of Hcy	None
Coelho Neto 2010 [19]	Brazil	PC	Patients with severe sepsis or septic shock	21	43.9	52.4	Within 24 h after ICU admission	NA	1 month	6	Difference of Hcy	None
Feng 2015 [22]	China	RC	Elderly patients with acute PE	210	71.3	52.4	At ICU admission	15 μmol/l	12 months	18	OR for mortality	Age, sex, PaO_2, SCr, peak TnI, DVT, comorbidities, and LVEF
Rahmani 2016 [34]	Iran	PC	Patients with severe traumatic brain injury	150	55.9	54.7	At ICU admission	NA	2 weeks	47	Difference of Hcy	None
Bernstein 2018 [35]	USA	RC	Patients with severe ICH	42	58.5	57.1	At ICU admission	NA	2 weeks	4	Difference of Hcy	None
Wexler 2018 [36]	USA	PC	Patients with sepsis	109	62	62	Within 48 h after ICU admission	NA	1 month	31	Difference of Hcy	None
Niu 2020 [24]	China	RC	Patients with severe multiple trauma	60	42.6	38.1	At ICU admission	15 μmol/l	6 months	25	Difference of Hcy and OR for mortality	Age, sex, cTnI, and PCT
Li 2020 [37]	China	RC	Patients with severe acute pancreatitis	164	57.4	65.8	At ICU admission	15 μmol/l	1 month	16	Difference of Hcy and OR for mortality	Age, sex, APACHE II Score, SCr, CRP, cTnI, and BNP
Chen 2020 [23]	China	RC	Patients with AECOPD and RF	97	74.8	68	At ICU admission	15 μmol/l	6 months	18	OR for mortality	Age, sex, and APACHE II Score
Zhang 2021 [39]	China	PC	Patients with AMI	109	62	62	Within 48 h after ICU admission	NA	12 months	23	Difference of Hcy	None
Liu 2021 [38]	China	RC	Patients with sepsis	352	58.8	59.4	At ICU admission	15 μmol/l	1 month	49	OR for mortality	Age, sex, SOFA score, CRP, SCr, and PCT
Chen 2021 [25]	China	RC	Patients with sepsis	60	79.1	51.7	At ICU admission	15 μmol/l	1 month	22	Difference of Hcy and OR for mortality	Age, sex, and SOFA score
Meng 2022 [26]	China	RC	Patients with severe multiple trauma	70	41.5	60.3	At ICU admission	15 μmol/l	6 months	30	Difference of Hcy and OR for mortality	Age, sex, APACHE II Score, D-dimer, and PCT

Hcy: Homocysteine; PC: Prospective cohort; RC: Retrospective cohort; MV: Mechanical ventilation; PE: Pulmonary embolism; ICH: Intracerebral hemorrhage; AMI: Acute myocardial infarction; AECOPD: Acute exacerbation of chronic obstructive pulmonary disease; RF: Respiratory failure; ICU: Intensive care unit; OR: Odds ratio; NA: Not applicable; PaO_2: Partial pressure of oxygen; SCr: Serum creatinine; cTnI: Cardiac troponin I; DVT: Deep vein thrombosis; LVEF: Left ventricular ejection fraction; PCT: Procalcitonin; CRP: C-reactive protein; BNP: B-type natriuretic peptide; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

▶ **Table 2** Study quality evaluation via the Newcastle-Ottawa Scale.

Study [Ref]	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Schindler 2000 [17]	1	1	1	1	0	0	1	1	1	7
Stoiser 2000 [18]	0	1	1	1	0	0	1	1	1	6
Tsantes 2010 [21]	1	1	1	1	0	0	1	1	1	7
Ploder 2010 [20]	0	1	1	1	0	0	1	0	1	5
Coelho Neto 2010 [19]	1	1	1	1	0	0	1	1	1	7
Feng 2015 [22]	0	1	1	1	1	1	1	1	1	8
Rahmani 2016 [34]	1	1	1	1	0	0	1	0	1	6
Bernstein 2018 [35]	0	1	1	1	0	0	1	0	1	5
Wexler 2018 [36]	1	1	1	1	0	0	1	0	1	6
Niu 2020 [24]	0	1	1	1	1	1	1	1	1	8
Li 2020 [37]	0	1	1	1	1	1	1	1	1	8
Chen 2020 [23]	0	1	1	1	1	1	1	1	1	8
Zhang 2021 [39]	0	1	1	1	0	0	1	1	1	6
Liu 2021 [38]	0	1	1	1	1	1	1	1	1	8
Chen 2021 [25]	0	1	1	1	1	1	1	1	1	8
Meng 2022 [26]	0	1	1	1	1	1	1	1	1	8

ference both > 0.05; ▶ **Fig. 3a and b**). Moreover, subgroup analyses suggested that the difference of serum Hcy between survivors and non-survivors were significant for studies with follow-up durations of 6–12 months, but not for those within 3 months (p for subgroup difference < 0.001; ▶ **Fig. 4a**). In addition, difference in study quality scores did not significantly affect the results (p for subgroup difference = 0.35, ▶ **Fig. 4b**).

Association between HHcy and mortality of critically ill patients

Seven retrospective cohort studies [22–26, 37, 38] with 1013 patients, all from China, evaluated the association between HHcy and all-cause mortality of the critically ill patients. Pooled results showed that HHcy at ICU admission was independently associated with a higher risk of all-cause mortality (OR: 2.99, 95 % CI: 2.26 to 3.97, p < 0.001; I^2 = 69 %; ▶ **Fig. 5a**). Sensitivity analyses by excluding one cohort at a time showed similar results (OR: 2.73 to 3.33, p all < 0.05). Moreover, subgroup analyses suggested that the association was stronger in studies with follow-up durations of 12 months (OR: 4.13, p < 0.001) and 6 months (OR: 3.38, p < 0.001) than those of 1 month (OR: 1.99, p < 0.001; p for subgroup difference < 0.001; ▶ **Fig. 5b**).

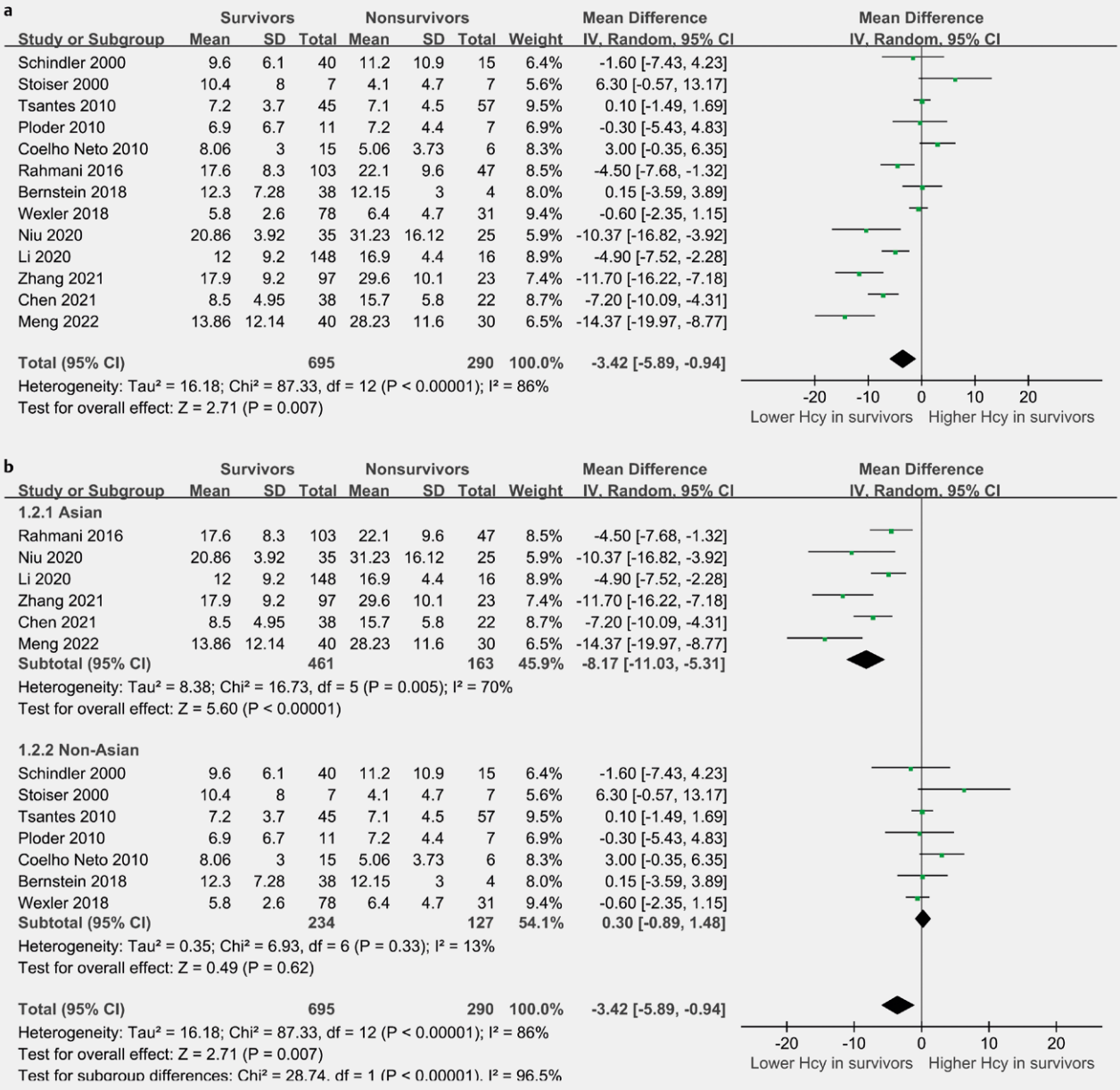
Publication bias

The funnel plots for the meta-analyses of Hcy difference and the association between HHcy and all-cause mortality are shown in ▶ **Fig. 6a, b**. On visual inspection, these plots were symmetrical, indicating low risks of publication biases. Egger's regression test also did not show significant publication biases (p = 0.22 and 0.27, respectively).

Discussion

In this meta-analysis, we pooled the results of 16 cohort studies and found that survivors of the critically ill patients admitted to ICU had a lower serum level of Hcy as compared to the non-survivors. Moreover, subsequent subgroup analysis showed that the difference of Hcy at ICU admission between the survivors and non-survivors were mainly observed in studies of the Chinese patients, but not for studies of the western countries. Additionally, meta-analysis of seven cohort studies, all from China, showed that HHcy defined as Hcy > 15 µmol/l was independently associated with a higher mortality risk in critically ill patients. Taken together, these results showed that a higher serum level of Hcy at ICU admission may be associated with an increased risk of all-cause mortality in critically ill patients, particularly in the Chinese population.

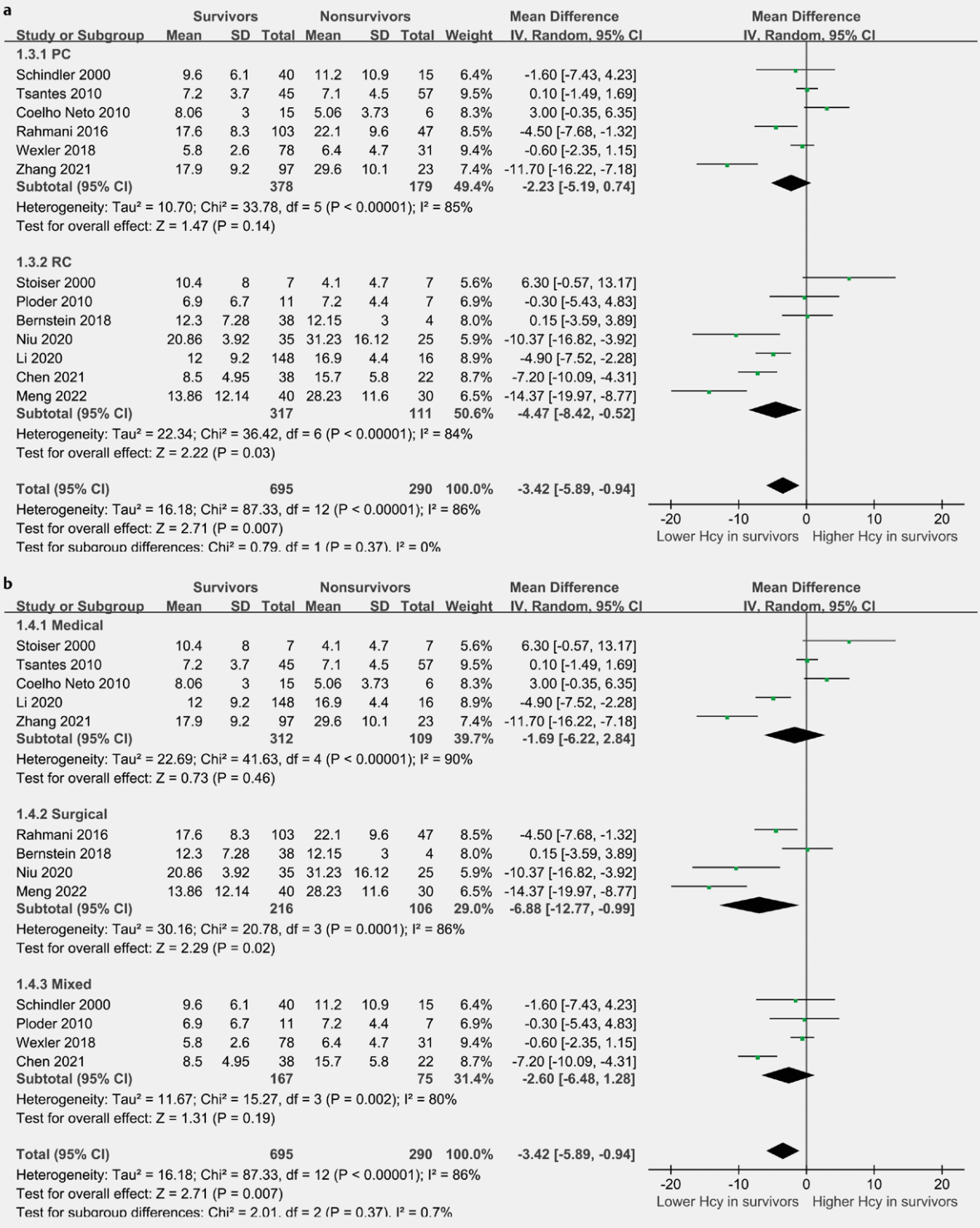
To the best of our knowledge, this is the first meta-analysis which evaluated the association between serum level of Hcy at ICU admission and all-cause mortality in critically ill patients. The strengths of the meta-analysis included the following. First, an extensive literature search was performed in five electronic databases to retrieve the up-to-date cohort studies regarding the prognostic role of Hcy in patients with critical illnesses. In addition, two outcomes of the meta-analyses were separately analyzed, which



▶ **Fig. 2** Forest plots for the meta-analysis comparing the difference of Hcy at ICU admission between survivors and non-survivors of critically ill patients. **a**: overall meta-analysis; and **b**: subgroup analysis in Asian and non-Asian patients.

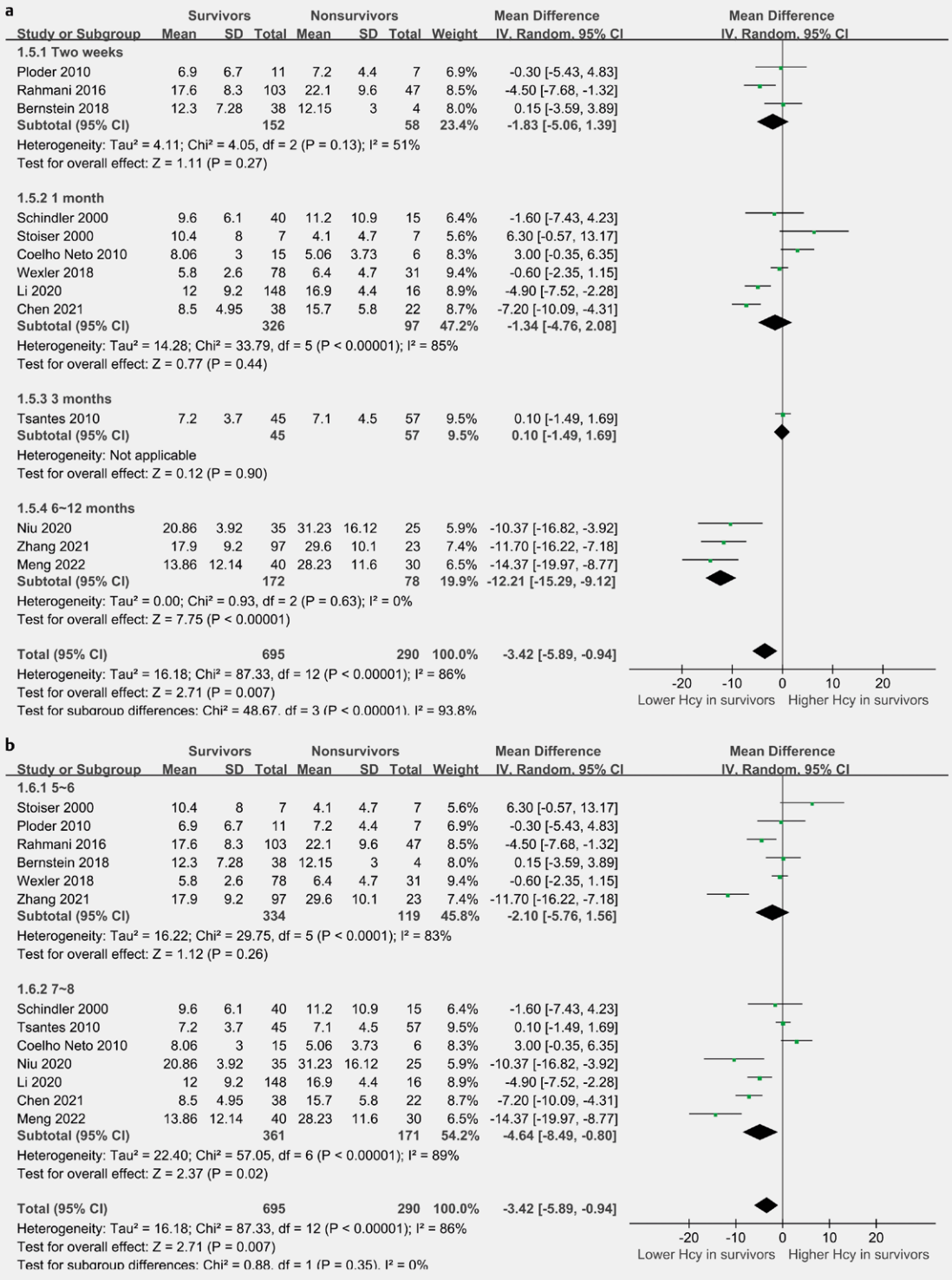
consistently showed that a higher Hcy at ICU admission is related with an increased risk of all-cause mortality in critically ill patients. Finally, sensitivity and subgroup analyses were performed, and the results validated the stability of the findings. The biological basis for the association between a higher serum level of Hcy and the increased mortality risk of patients with critically ill remains not determined. Moreover, currently, it remains unknown whether Hcy is actively involved in the pathogenesis and exacerbation of the critical illnesses, or it is just a simple biomarker of disease severity. A previous showed that HHcy in patients with critical illnesses was associated with the deficiency of pyridoxal-5′-phosphate, a maker of increased catabolism and reduced body reserve [40, 41]. Moreover, a higher serum level of Hcy has been associated with overactivated inflammation [42], oxidative stress [43], and endothelial dysfunction [44], all of which have been associated with the poor prognosis in patients with critical illnesses. Besides, Hcy has been related to the hypercoagulative status and increased risk of thrombosis [45], myocardial injury [46], and acute kidney injury [47] in patients with critical illnesses, all of which could adversely affect the prognosis of the patients. Studies are warranted to determine the molecular mechanisms underlying the influence of Hcy on mortality in patients with critical illnesses.

Our subgroup analyses showed that the difference between Hcy at ICU admission between survivors and non-survivors of critically



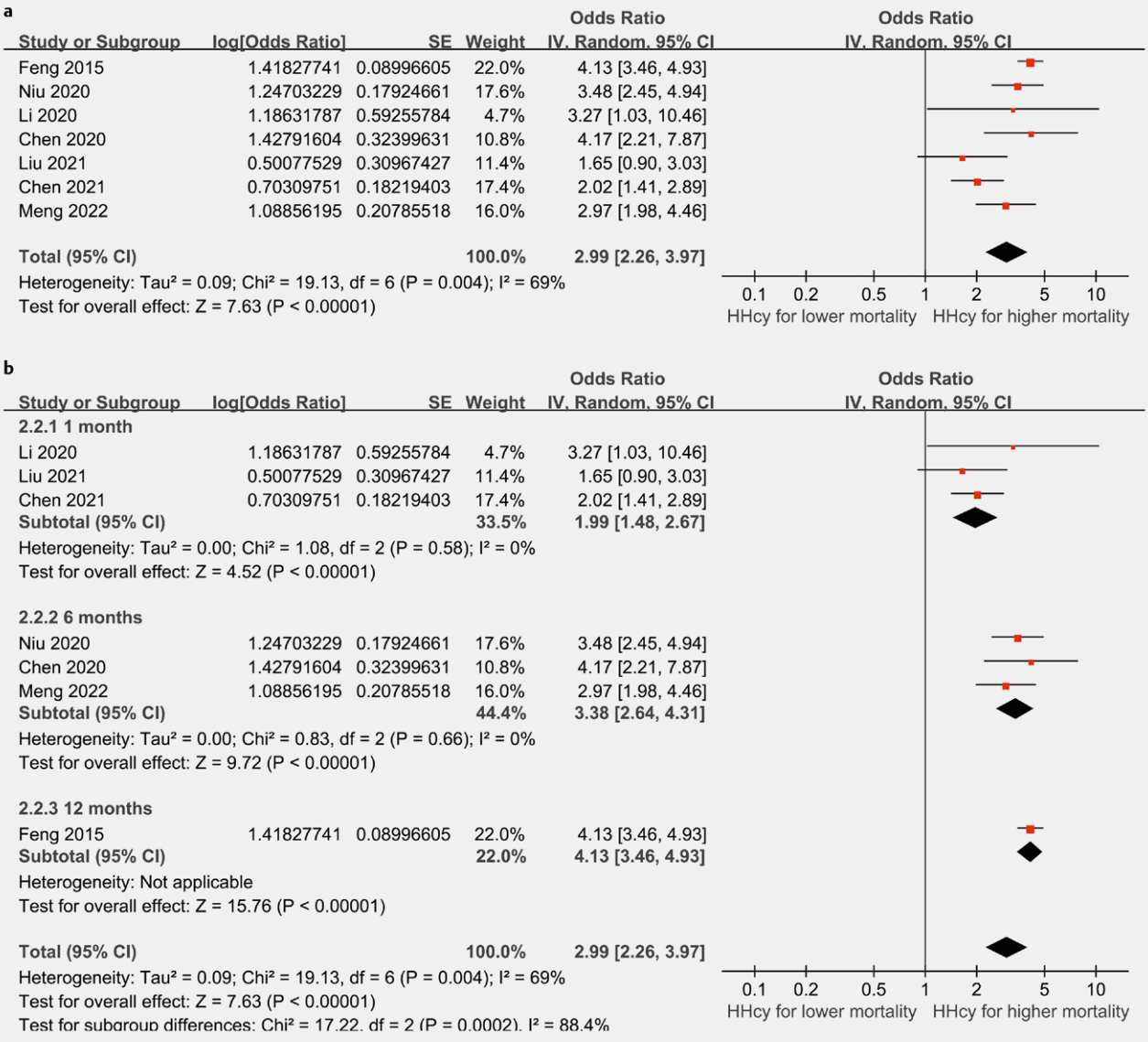
▶ **Fig. 3** Subgroup analyses comparing the difference of Hcy at ICU admission between survivors and non-survivors of critically ill patients. **a**: subgroup analysis according to study design; and **b**: subgroup analysis in patients with medical ICU, surgical ICU, and any ICU.

ill patients was significant in Asian patients (mostly from China), but not in patients from the western countries. Moreover, pooled results of seven cohorts, all from China, showed that HHcy may be an independent risk factor of higher mortality risk in patients with critically illnesses. These results may suggest that the association between higher serum level of Hcy and increased mortality risk of the critically ill patients was mainly observed in Chinese population. The reasons for the possible racial difference of the associa-



▶ **Fig. 4** Subgroup analyses comparing the difference of Hcy at ICU admission between survivors and non-survivors of critically ill patients. **a**: subgroup analysis according to the follow-up duration; and **b**: subgroup analysis according to the different quality scores.

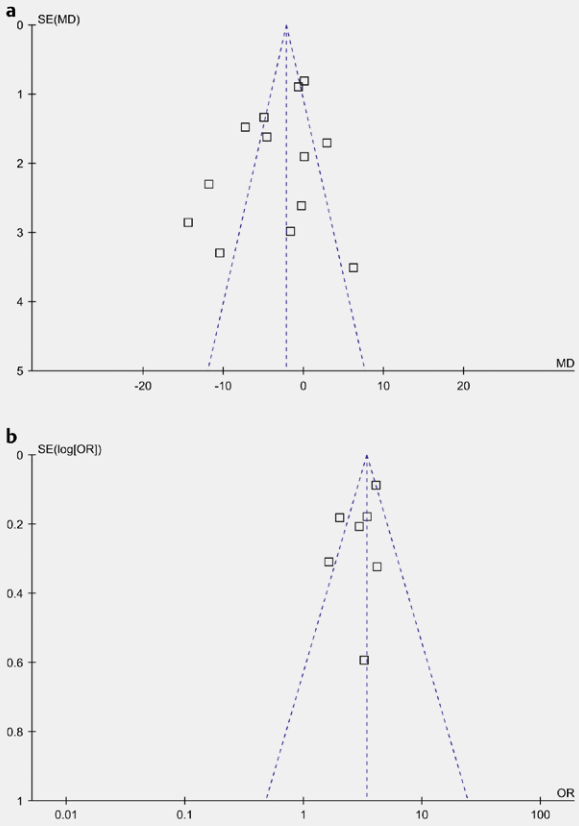
tion between Hcy and mortality risk in patients with critical illnesses are also unknown. Previous studies have suggested a possible racial difference of the serum level of Hcy [48, 49]. The prevalence of HHcy may be higher in Chinese population than that of the western population probably because of low vitamin B in the Chinese population due to the low-vegetable diet [50]. Moreover, genetic factors, such as the prevalence of the Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism may also affect the



▶ **Fig. 5** Forest plots for the meta-analysis of the association between HHcy and all-cause mortality of critically ill patients. **a**: overall meta-analysis; and **b**: subgroup analysis according to the follow-up durations.

association between Hcy and mortality risk in the critically ill patients from different ethnicities [51]. The mutation of the MTHFR gene which causes the C677T polymorphism could lead to the reduced activity of the MTHFR enzyme. Accordingly, the homozygous mutated subjects have higher Hcy levels while the heterozygous mutated subjects have mildly raised Hcy levels compared with the normal, non-mutated controls [51]. As for the potential difference for the prevalence of this variant different between Asians (Chinese) and people from western countries, it was still to be determined because limited data is available [51]. In addition, results of subgroup analyses also suggested that the difference of Hcy is significant in non-survivors and survivors observed at 6–12 months, but not for those observed within 3 months. In addition, the association between HHcy and mortality is also stronger at 6–12 months, than that at 1 month. All of these findings may suggest a chronic adverse influence of HHcy on mortality in critically ill patients, rather than an acute effect. Studies are needed in the future to validate these findings and to clarify the possible mechanisms.

This meta-analysis also has some limitations, which should be considered when the results are interpreted. First, although all of the included patients were with critical illnesses and admitted to the ICU, the diagnosis and treatments for the patients were different, which may lead to the heterogeneity. Besides, only serum level of Hcy at ICU admission was analyzed. It remains unknown whether the changes of Hcy during ICU stay, or hospitalization may affect the association between Hcy and mortality in these patients. Moreover, the seven cohort studies in the meta-analysis for the association between HHcy and all-cause mortality in critically ill patients were all retrospective, the results of which may be confounded by the selection and recall biases. Finally, as previously mentioned, a



▶ **Fig. 6** Funnel plots for the publication bias underlying the meta-analyses. **a**: funnel plots for the publication bias underlying the meta-analysis for the difference of Hcy between survivors and non-survivors of critically ill patients; and **b**: funnel plots for the publication bias underlying the meta-analysis for the association between HHcy and all-cause mortality of critically ill patients.

causative relationship between HHcy and all-cause mortality in patients with critical illnesses could not be derived because this is a meta-analysis of observational studies. Clinical studies may be considered to evaluate the possible influence of Hcy-lowering therapy on the prognosis of critically ill patients with HHcy.

In conclusion, results of this meta-analysis showed that a higher serum level of Hcy at ICU admission may be associated with an increased risk of all-cause mortality in critically ill patients, particularly in the Chinese population. Future studies are needed to determine the underlying mechanisms and to investigate whether Hcy-lowering therapy could improve the survival of these patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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