The role of mHLA-DR in the early diagnosis of sepsis patients with severe trauma: a meta-analysis

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Research

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Abstract

Background

HLA-DR is a common and significant biomarker in sepsis. However, as a biomarker of post-traumatic sepsis, there are few studies. This meta-analysis was conducted to evaluate the value of HLA-DR in the diagnosis of severe traumatic sepsis.

Methods

We developed a strategy for literature retrieval from the PubMed, MEDLINE, Web of Science, EMBASE, and Cochrane Library databases. All studies published until June 1, 2021, were retrieved. All studies that were included considered HLA-DR in the diagnosis of adult post-traumatic sepsis, and each study calculated the sensitivities and specificities.

Results

The study included 8 articles involving 639 trauma patients. combined sensitivity was 0.81 (95% CI, 0.75–0.86), the combined specificity was 0.67 (95% CI, 0.62–0.71), the positive likelihood ratio was 2.29 (95% CI, 1.73–3.04), and the negative likelihood ratio was 0.32 (95% CI, 0.23–0.44). The area under the summary receiver operating characteristic curve was 0.84 (95% CI, 0.80–0.87), and the Q index was 0.76. The combined diagnostic odds ratio was 9.11 (95% CI, 5.37–15.45).

Conclusions

The results of this meta-analysis showed that HLA-DR could be considered as a useful biomarker for the early diagnosis of severe traumatic sepsis. Its sensitivity and diagnostic abilities are excellent. However, its specificity is inadequate. Therefore, it should be combined with other clinical indicators to assess post-traumatic sepsis, and cannot be used in the diagnosis of a disease alone.

Background

Trauma is a complex disease involving multiple organs, systems, and tissues, and the injury caused by trauma and surgery can disturb the balance of the inflammatory and anti-inflammatory response. On the one hand, it causes organic organ damage, while on the other hand, it increases the risk of developing sepsis and related complications (organ dysfunction). Its pathophysiological process is regulated mainly by the neuroendocrine immune network, and it involves a variety of inflammatory mediators, cytokines, neurotransmitters, hormones, and other effector molecules. It is a grave threat to human health and has gained prominence as the main cause of death in young people under 45 years old [1]. Three peaks in the mortality rate caused by trauma were observed; 53% was attributable to the accident scene (death

occurring immediately after injury), 7.5% was reported in the emergency department (occurring within a few hours after injury), and 39.5% was documented in the hospital (occurring days or weeks after injury), with 80% of the hospital deaths being caused by sepsis or multiple organ failure [2]. With the progress achieved in the medical field, the overall mortality of trauma patients has considerably reduced; however, the incidence rate of sepsis after trauma remains high [3]. Therefore, the early prediction of traumatic sepsis and the implementation of early interventions in high-risk patients are key in the reduction of the incidence of sepsis and in the improvement of the prognosis of patients [4]. Presently, the gold standard for the diagnosis of traumatic sepsis is the conduction of blood bacterial culture, which demonstrates the disadvantages of being laborious and time-consuming with low positive rates and contamination by environmental factors. Concurrently, patients with traumatic sepsis do not display characteristic features in the early stages; thus, they cannot be diagnosed and treated early and accurately in the early stages, which leads to the low success rate of trauma treatment and cure [5]. Therefore, the establishment of a reliable early warning index with high specificity and sensitivity for post-traumatic sepsis is necessary. Moreover, the established method should be economic and convenient with the achievement of rapid results. Presently, there are many studies available on the early prediction of sepsis, but few studies have focused on traumatic sepsis. The main indicators used in the prediction of traumatic sepsis are biomarkers, demographic characteristics of patients (such as age, gender, and race), injury characteristics (such as injury severity, injury mechanisms, number of injuries, age, age, gender, and race), genetic factors, and mathematical prediction models based on substantial data.

HLA-DR is an MHC-II molecule, which is expressed on monocytes, B lymphocytes, activated T lymphocytes, macrophages, human progenitor cells and activated NK lymphocytes. In 1986, Polk and colleagues pioneered the discovery of the association between the occurrence of sepsis and low mHLA-DR expression [6]. Presently, the conclusion of most studies is consistent. The change of HLA-DR expression is related to the course of the disease and the prognosis of post-traumatic patients. Furthermore, it not only helps predict the occurrence of post-traumatic sepsis, but also aids the prediction of the therapeutic effect.

Sepsis remains the main cause of death of trauma patients in the hospital. This creates emotional and economic burdens for the family and society. Therefore, it is important to develop a timely and effective method for the diagnosis of post-traumatic sepsis. The findings of this study will be of importance to clinical practice.

Therefore, this meta-analysis was conducted to evaluate the value of HLA-DR in the diagnosis of severe traumatic sepsis. This study is registered with PROSPERO, number CRD42021246624.

Methods

Based on the recommendations and the quality of reports of meta-analyses (QUOROM) statement, we developed the protocol prior to conducting this study [7]. Because all the analyses are based on previous published articles, this study did not require ethical review or the consent of the patients' families.

Search Strategy

We developed a strategy for the retrieval of literature from databases including the Cochrane Library, PubMed, EMBASE, MEDLINE and Web of Science. All studies published until July 1, 2021 were retrieved; the key words of the literature search were “trauma or injury” and “sepsis or infection” and “HLA-DR”. Simultaneously, screen the retrieved documents to identify relevant studies that meet the criteria.

Eligibility Criteria

The articles included in this meta-analysis meet the following criteria : articles should be related to the diagnosis and biomarkers of traumatic sepsis; clear criteria should be available for the diagnosis of sepsis; and data should be complete, including data on the specificity and sensitivity of biomarker-based diagnoses and the number of cases in the control and disease groups. The exclusion criteria were as follows: the subjects should be under 18 years of age, pregnant, presenting with immune system and blood system diseases, and prescribed with immune system-related drugs before infliction of the injury; the types of research articles excluded were comments, case reports, letters, abstracts, or agreements; and the study should be a repetition of a previously reported study.

The article was selected by two independent reviewers (GSC, DLW.) according to established standards. When they presented with different opinions, the participation of a third-party reviewer (AQZ) was sought in the review and joint decisions were formulated to ensure the reliability of the included articles and to reduce the generation of bias and heterogeneity in the publications.

Data Extraction

Two researchers (JCQ, QW) evaluated and extracted the data according to the data extraction table. In the event of a disagreement, involvement of the third party (PGX,JD) was sought, and four researchers worked together to reach a consensus. The contents of the data extraction form included the following: basic information of the article including the year of publication, the country, and the first author; and data including the number of cases in the control and disease groups, as well as the sensitivity and specificity of biomarker diagnoses. If necessary, the author (JD) supplementary data obtained by contacting researchers who have published studies.

Statistical Analysis

In this study, data on the numbers of true positives (TPs), true negatives (TNs), false positives (FPs) and false negatives (FNs) were extracted from each study. The sensitivities, specificities, diagnostic odds ratios (DOR)s, negative likelihood ratios (NLRs), and positive likelihood ratios (PLRs) were then calculated to evaluate the data. We also constructed the summary receiver operating characteristic (SROC) curves and calculated the area under the curves (AUCs), 95% CI, and the Q index. The heterogeneity test was determined by whether the "shoulder arm" phenomenon existed at the threshold of the SROC curve as well as along with the I^2 value of the heterogeneity results of the non-threshold effect. I^2 values approaching zero (0%) indicated no observed heterogeneity and larger values increasing heterogeneity. $I^2 > 25\%$

indicated a lack of heterogeneity, allowing to use the fixed-effects model; otherwise, the random-effects model was used. The Deek's funnel plot was used to test the publication bias, and a P value greater than 0.05 indicated that the results were reliable and that there was no publication bias.

All statistical analyses were performed using STATA (15.1 version; StataCorp, College Station, TX, USA), Meta-DiSc (1.4 version) [8], and RevMan (5.3 Vision; The Cochrane Collaboration, UK). A P value of less than 0.05 was considered statistically significant.

Results

Study Characteristics

Data on a total of 1516 studies were obtained from PubMed, MEDLINE, Web of Science, EMBASE, and the Cochrane Library databases. Of these, 550 repetitive studies and 879 unqualified products were excluded. The remaining 35 studies were screened and finally, eight studies met the inclusion criteria for the meta-analysis (Fig. 1). There were five articles on post-traumatic sepsis and three articles on post-surgical sepsis [9–16]. The data of each study and basic information are shown in **Table 1**. The eight clinical prospective cohort studies included patients from the emergency department, surgery, and ICU. The study population comprised adults, patients admitted eight hours after trauma, and patients hospitalized for at least 14 days after surgery. Of the 639 patients who experienced trauma and underwent postoperative surgery, 234 presented with sepsis. The blood samples were subjected to analysis on the day of blood collection and the results of the corresponding tests were obtained. Seven studies used flow cytometry (FCM) to detect mHLA-DR expression and one study used droplet digital PCR. The trend in mHLA-DR expression was similar. In addition to the eight articles, there were also other cohort studies that considered HLA-DR as a biomarker for traumatic sepsis. All results showed that compared to the expression in healthy people, the expression of mHLA-DR after trauma was reduced, and that the expression of mHLA-DR in patients with sepsis was significantly lower than that in patients without sepsis. In seven studies, the optimal cutoff point based on the ROC curve was calculated. However, we did not get consistent results. The results of the QUADAS-2 literature quality evaluation are shown in Fig. 2.

Quantitative Data Synthesis

The merged sensitivities and specificities were 0.81 (95% confidence interval, 0.75–0.86) and 0.67 (95% confidence interval, 0.62–0.71), respectively. (Fig. 3). The merged PLR was 2.29 (95 % CI, 1.73–3.04), and the merged NLR was 0.32 (95 % CI, 0.23–0.44) (Fig. 4). The area under the SROC curve of the mHLA-DR expression was 0.83, and the Q* value was 0.76, which indicated a high level of diagnostic accuracy (Fig. 5). The SDOR was 9.11 (95 % CI, 5.37–15.45) (Fig. 6). We also performed a subgroup analysis of five post-traumatic sepsis studies. The merged sensitivities, specificities, PLRs, NLRs, and SDORs of the mHLA-DR were 0.81 (95 % CI, 0.73–0.87), 0.60 (95 % CI, 0.54–0.66), 1.90 (95 % CI, 1.55–2.33), 0.35 (95 % CI, 0.21–0.57), and 6.50 (95 % CI, 3.82–11.07), respectively. The area under the SROC curve for mHLA-DR expression was 0.76, and the Q* value was 0.70, indicating good diagnostic accuracy.

Investigation of Heterogeneity

We used the Cochran Q test and the I² statistic to determine the presence of statistical heterogeneity. Significant heterogeneities were observed for the pooled sensitivities, specificities, PLRs, NLRs, and SDORs. Therefore, we performed a threshold analysis to explore the effect (Spearman correlation coefficient = 0.659, $P = 0.076$) and found that there was no statistically significant differences. Therefore, a symmetrical model was selected to construct the SROC curve, and since there was no “shoulder arm” phenomenon, it further verified that there was no threshold effect in this study (Fig. 5).

According to the Cochran’s Q test for DOR, the Cochran’s Q value was equal to 9.22 and the P value was equal to 0.24, which implied that, in this study, the heterogeneity was attributable to the non-threshold effect. Furthermore, the merged sensitivities, specificities, and PLRs were greater than 50%. The existence of non-threshold effect heterogeneity is further clarified in Figs. 3 and 4.

Deek’s Publication Bias Test

The stability of the results was based on the linear regression method to test whether the Deek’s Funnel plot was symmetric. The Stata software (15.1 version) was selected to test the publication bias of the data in this study. The results showed that the Deek’s Funnel plot was symmetric, and that there was no publication bias ($P = 0.37$) (Fig. 7).

Discussion

HLA-DR has been used widely in clinical and basic scientific research, such as the diagnoses of sepsis [11] and the prediction of prognoses [17]. It is used to evaluate the severity and prognosis of burns [18] and to evaluate the immune function of patients after surgical operations; however, thus far, it has not been used in the diagnoses and predictions of disease prognoses.

All 639 patients included in the eight studies met the inclusion and exclusion criteria. In 7 studies, the expression of mHLA-DR was detected using flow cytometry, and in one study, droplet digital PCR was used.

In the first five studies included, the patients in the trial group were admitted within eight hours of blunt trauma, and were hospitalized for 14 to 28 days. All patients were diagnosed with sepsis in accordance with the guidelines of the American College of Chest Physicians/Society of Critical Care Medicine consensus conference [19], with the gold standard for the diagnosis of sepsis being the detection of SIRS plus-positive bacterial cultures. All studies evaluated the mHLA-DR expression in patients in the first 14 days. In three studies conducted by Cheron et al. in 2010, 2012, and 2015, the characteristics of all patients in the experimental group were similar. All patients presented with ISS scores ≥ 25 and had been treated in the ICU. The results of these three studies showed that there were significant differences in the expression of mHLA-DR between patients with sepsis and patients without sepsis, and that the ratios of the expression on days three to four compared with those on days one to two had the highest specificities

and sensitivities, with 1.2 being the best cut-off value. Vester et al. studied 24 patients with multiple traumas and compared the occurrence of SIRS, sepsis, and MODS in patients with blunt trauma; eight postoperative patients were considered as the control group. Compared with the patients without MODS, the MFIs of five patients with MODS decreased more on the 3rd and 7th days. In the 17 patients with SIRS, the MFIs decreased on day 3 and increased significantly on day 7 and day 14. Compared with patients without sepsis, the MFIs of patients with sepsis decreased on the 3rd and 7th days after trauma and increased significantly on the 14th day. In our analysis, we used the MFIs of the third day as the cut-off value to diagnose sepsis. Nine patients with SIRS were deemed false-positive, and no false negative cases were found. The sensitivity was high; however, the specificity was low. Ditschkowski et al. not only detected HLA-DR in the monocytes from 1 to 14 days after injury, but they also detected T lymphocytes and soluble HLA-DRs. When the average fluorescence intensity of HLA-DR on T cells measured at channel 161 on the first day was considered as the cut-off value, the sensitivity and specificity for predicting sepsis were 67% and 72%, respectively. Using the cut-off value of the average fluorescence intensity of HLA-DR detected in channel 90 on the second day, the sensitivity and specificity for predicting sepsis were 53% and 76%, respectively. The sensitivity and specificity of detecting the concentration of soluble HLA-DR at 0, 1, 2, 4, and 6 days after injury were 72% and 90%, respectively. Ditschkowski et al. also conducted another study in the same year and found that the sensitivity and specificity for predicting sepsis were 69% and 77%, respectively, when the average fluorescence intensity of HLA-DR in channel 155 on day six was considered as the cut-off value [20]. The patients studied by Vester et al. and Ditschkowski et al. presented with an ISS ≥ 16 . These five studies also showed that the expression of HLA-DR in patients with different degrees of trauma was also significantly different.

In addition to the above-mentioned studies, we also identified other studies that investigated the prediction of post-traumatic sepsis using HLA-DR [21–23]. In these studies, we observed consistent changes in HLA-DR after trauma and sepsis. These studies provided us with a new direction for the early warning of traumatic sepsis, viz., the expression of B cells, T cells, monocytes, and soluble HLA-DR in post-traumatic patients could be considered to explore and establish an optimal cut-off value, and might be combined to predict the occurrence of sepsis.

The other three studies included were studies conducted on sepsis after surgery. In the study reported by Almansa et al., data on PCT and HLA-DR gene expression were combined to detect sepsis in 154 patients after their surgeries and the HLA-DR expression was quantified using droplet digital PCR. Sepsis-3 criteria was the gold standard for all patients [24]. When PCT alone was used to predict sepsis, the optimal cutoff value was 1.115 ng/ml, the sensitivity was 73.3%, and the specificity was 75.5%. If PCT combined with HLA-DR was used to predict sepsis, then the ratio of PCT concentration and mHLA-DR concentration was used to predict sepsis. The OOP (optimal operating point) was 0.0003 and the specificity and sensitivity were 75.5% and 80.2%, respectively, indicating that the use of combined predictors could help improve the accuracy of sepsis diagnosis significantly. In the study reported by Asadullah et al. involving 57 neurosurgical patients, blood samples were collected one day before the operation and one to six days after operation. Fourteen patients developed postoperative infection complications. The predictive value of HLA-DR expression of less than 30% for postoperative infection

was 0.9. Strohmeyer et al. studied 56 patients subjected to cardiac surgery involving cardiopulmonary bypass, In this study, using a cutoff of 5792 HLA-DR molecules per cell, the sensitivities and negative predictive values of IL-10 and IL-10 combined with HLA-DR expression were found to be 1.0, while the sensitivities and specificities of IL-10 and IL-10 combined with HLA-DR expression were 0.75 and 0.84, 0.75 and 0.94, respectively. Cheadle [25] and Albertsmeier [26] also studied the relationship between HLA-DR and postoperative sepsis. The findings of the studies on postoperative sepsis, and the changes in HLA-DR after surgery and sepsis were consistent.

The analysis of the studies showed that HLA-DR could be considered a useful indicator for the prediction of post-traumatic sepsis, with good sensitivity but low specificity; therefore, our research focus was the combination of other indicators, including clinical indicators and biomarkers, and the use of genomics, proteomics, metabolomics, and bioinformatics research methods to explore early biomarkers, to establish an accurate early warning system for post-traumatic sepsis. Although these findings warrant prospective multi center large sample size verification, we suggest that there is potential applicability in clinics to further improve the success rate of the treatment of traumatic sepsis.

There were some limitations encountered in the present study. First, we searched for relevant literature in various databases, and while many articles met the screening criteria, data of only eight articles were extracted with five articles published on blunt trauma sepsis and three published on surgical trauma sepsis. All of these data are published in English, which will lead to the lack of relevant research data in other languages. Second, in our meta-analysis, no common heterogeneity of the threshold effect was observed; however, heterogeneity of the non-threshold effect could be observed. These studies differed in several ways (e.g., clinical spectra of patients, age, gender, type of admission, and the mHLA-Dr analysis used). There was heterogeneity in the clinical data because of certain unchangeable factors. Third, a few studies used different gold standards to diagnose sepsis. Fourth, while the methodological quality of each study was acceptable, there was only one study with statistical heterogeneity. The statistical heterogeneity of the results was tested by constructing a Galbraith diagram (Fig. 8). However, none of the included studies met the QUADAS-2 criteria completely.

Conclusions

HLA-DR is a significant indicator in the prediction of post-traumatic sepsis, with high sensitivity, but presents a lack of specificity; therefore, HLA-DR cannot be used as an independent indicator in the diagnosis of post-traumatic septicemia. It is also necessary to consider a high specificity index for stating a combined early warning of traumatic sepsis with the actual clinical situation for comprehensive judgment.

Abbreviations

ABC: antibody binding capacity; AUC: area under the curve; CI: confidence interval; DOR: diagnostic odds ratio; FCM: flow cytometry; HLA-DR: human leukocyte antigen DR; ICU: intensive care unit; ISDC:

International Sepsis Definition Conference; MFI: melt flow index; MODS: [multiple organ dysfunction syndrome](#), NLR: negative likelihood ratio; QUADAS: quality assessment of diagnostic accuracy studies; PLR: positive likelihood ratio; ROC: receiver operating characteristic; SDOR: summary diagnostic odds ratio; SIRS: systemic inflammatory response syndrome; SROC: summary receiver operating characteristic curve.

Declarations

Ethics approval and consent to participate

Since all analyses were conducted based on previously published articles, this study did not require ethical review or the consent of the patients' families.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GSC designed the experiments, collected the data, and drafted and revised the manuscript; JD guided the design of the study; AQZ revised the manuscript; DLW, JD and JCQ collected, analyzed, and interpreted the data; GXP and QW performed statistical analysis. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow diagram of the study selection process.

Figure 2

Risk of bias summary

Figure 3

Forest plots of the sensitivity and specificity of HLA-DR of all included studies. The solid circles represent each individual study, and the solid diamonds represent the pooled diagnostic odds ratios. The sizes of the circles are proportional to the sizes of the included studies. Error bars are 95% CIs. df = degrees of freedom.

Figure 4

Forest plots of the positive likelihood and negative likelihood ratios (LR) of HLA-DR of all included studies. The solid circles represent individual studies, and the solid diamonds represent the pooled diagnostic odds ratios. The sizes of the circles are proportional to the sizes of the included studies. Error bars are 95% CIs. df = degrees of freedom

Figure 5

Summary receiver operating characteristic (SROC) curve of all included studies. The circles represent individual studies in the meta-analysis. The sizes of the circles are proportional to the size of the corresponding included study. AUC = area under the curve.

Figure 6

Summary diagnostic odds ratios (ORs) of HLA-DR of all included studies. The solid circles represent individual studies, and the solid diamond represents the pooled diagnostic OR. The size of each circle is proportional to the size of the corresponding included study. Error bars are 95% CIs. df = degrees of freedom.

Figure 7

Deek's Funnel plot.

Figure 8

Galbraith diagram.