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Monocyte distribution width (MDW) as a reliable diagnostic biomarker for sepsis in patients with HIV

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ABSTRACT

Sepsis is a leading cause of death among patients with HIV, but early diagnosis remains a challenge. This study evaluates the diagnostic performance of monocyte distribution width (MDW) in detecting sepsis in patients with HIV. A prospective observational study was conducted at Shanghai Public Health Center, involving 488 hospitalized patients with HIV aged 18–65 between December 2022 and August 2023. MDW was measured at admission, and its diagnostic accuracy was compared with Sepsis-3 criteria. Survival rates on day 28 and 90 were also recorded. Additionally, five machine learning (ML) models were tested to enhance diagnostic efficacy. Of 488 subjects, 90 were in the sepsis group and 398 in the control group. MDW showed a diagnostic area under the curve (AUC) of 0.82, comparable to C-reactive protein (CRP) and Procalcitonin (PCT) with AUCs of 0.78 and 0.82, respectively. With a cut-off value of 25.25, MDW had a sensitivity of 0.83 and specificity of 0.76. The positive and negative predictive values were 44% and 95%, respectively. When MDW was combined with platelet count, serum albumin, and hemoglobin in a random forest model, the AUC improved to 0.931. The model achieved a sensitivity of 1.00 and specificity of 0.732. MDW is a useful diagnostic marker for sepsis in patients with HIV, with strong sensitivity and specificity. Combining MDW with other lab markers can further enhance diagnostic accuracy.

Trial registration: ClinicalTrials.gov identifier: NCT05036928..

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KEYWORDS Biomarkers; human immunodeficiency virus (HIV); monocyte distribution width (MDW); sepsis; Sepsis-3

Introduction

HIV infection continues to pose a significant public health challenge. While antiretroviral therapy (ART) has improved the life expectancy of patients with HIV to nearly match that of uninfected individuals, many progress to advanced immunodeficiency due to late diagnosis or lack of access to ART [1]. Patients with HIV are prone to develop sepsis from various opportunistic infections. Sepsis is manifested as life-threatening organ dysfunction caused by a dysregulated host response to infection [2]. In patients with HIV, the mortality rate from sepsis is 28% higher than that in those uninfected [3].

A major challenge currently is the early and accurate diagnosis of sepsis. Currently, there is no gold standard for the diagnosis of sepsis [4–6]. The most widely accepted diagnostic method utilizes the Sepsis-3 criteria, which are recognized for their high diagnostic efficacy [7]. However, this standard has several limitations, including a complex assessment process and lengthy time requirements [8]. The Sepsis-3 diagnostic process includes two steps: identifying an infection and assessing organ dysfunction using the Sequential Organ Failure Assessment (SOFA) score. SOFA assesses the function of six organ systems: respiratory, coagulation, liver, cardiovascular, central nervous system, and renal function, with each system scored from 0 to 4. Sepsis is diagnosed if there is an infection and a 2-point or greater increase in the SOFA score [9].

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Monocytes, which serve as the first line of defense against pathogens, undergo several changes in number, morphology, phenotype, and function during disease progression, which correlate with clinical outcomes [10]. Monocyte Distribution Width (MDW), as an important biomarker, has been shown in studies to be valuable in the diagnosis and prognosis of sepsis, post-cardiovascular surgery sepsis, COVID-19, chronic liver disease, urinary sepsis, and others. It is significantly correlated with inflammatory markers such as CRP and fibrinogen and can significantly improve the diagnostic accuracy of various diseases [11–17]. Research has demonstrated that MDW greater than 20.5 significantly aids in the diagnosis of sepsis in HIV-negative populations [18, 19]. It is known that monocytes display activated phenotypes during HIV-infection [20]. Whether the MDW could serve as a biomarker of sepsis in patients with HIV has not yet been explored and warrants further investigation.

Machine learning (ML) offers a promising approach to sift through vast clinical data sets to identify significant patterns and develop predictive models more effective than traditional methods [21, 22]. In this study, we aimed to evaluate MDW in diagnosis of sepsis in patients with HIV and utilized ML to select indicators from multiple clinical data sources, including MDW, and developed a diagnostic model to further improve the diagnostic efficacy of sepsis in patients with HIV.

Methods

Study design and participants

This investigation is a single-center, prospective cohort study consecutively involving patients hospitalized in the Department of Infection and Immunology at the Shanghai Public Health Clinical Center from December 2022 to September 2023. This study has been registered on ClinicalTrials.gov [registration number NCT05036928). The inclusion criteria are as follows: (1) aged 18–65 years; (2) hospitalized patients tested positive for HIV-1; (3) patients who voluntarily sign an informed consent form and can commit to follow-up visits. Exclusion criteria include: (1) pregnancy or breastfeeding; (2) active substance use (drugs or alcohol); (3) severe comorbidities that may compromise study compliance or data validity.

Test methods and data collection

Following patient consent, clinical physicians ordered relevant blood tests. For this study, we utilized residual blood samples from clinical diagnostic tests performed on the first day of the patient's hospitalization for measuring MDW; no additional blood collection was required from the patients. Samples were collected using K_2EDTA tubes and processed on the DxH900 hematology analyzer (Beckman Coulter Inc.) within 3 h of collection at room temperature, with each test requiring 0.5 ml of sample. The DxH900 is maintained, calibrated, and operated according to the manufacturer's specifications. The analyzer uses Volume, Conductivity, and Scatter technology to measure MDW. This technology provides detailed analysis of cell morphology, size, granularity, and internal structure by measuring cell volume, conductivity, and scatter, thereby offering rich data on the cell's condition.

We selected the Sepsis-3 criteria as the reference standard for diagnosis due to its higher sensitivity and specificity, which better reflect the current understanding of the pathophysiology of sepsis and its widespread acceptance and validation in clinical practice. In the subgroup analysis, we categorized patients into a viremia group (HIV viral load ≥1000 copies/mL) and a non-viremia group (HIV viral load <1000 copies/mL) based on the World Health Organization criteria, using 1000 copies/mL as the threshold, and conducted further analyses accordingly [23]. Clinical data and results from the reference standard were concealed from the operators conducting the index test. Similarly, clinical information and outcomes of the index test were not accessible to the evaluators of the reference standard. This approach ensures an unbiased assessment by preventing any potential influence of clinical information on the diagnostic process.

This study collected clinical data using a case report form (CRF). For each patient, the following data were extracted from electronic medical records: basic demographic characteristics (age, gender), vital signs at admission (heart rate, respiratory rate, etc.), laboratory test results (complete blood count, blood biochemistry, C-reactive protein [CRP], Procalcitonin [PCT], etc.), HIV-related parameters (time of HIV diagnosis, whether to use ART, HIV viral load, $CD4^+$ T cell count, $CD4^+$T cell/$CD8^+$T cell ratio), SOFA score at admission, causative pathogens (bacteria, viruses, and fungi, etc.), comorbidities, and outcomes on day 28 and 90 post-admission (mortality or survival).

Machine learning model building

To sift through complex datasets and enhance diagnostic accuracy, we developed ML models. The specifics are as follows: For the feature selection, we selected the variables that are statistically significantly different among two groups (sepsis vs. control). To investigate whether multicollinearity existed among variables, Spearman correlation analysis was performed to identify variables with high correlations.

For the ML model building, the cohort was divided into two datasets, 80% as a training set and 20% as a

testing set. The training set uses fivefold cross-validation, which divides the dataset into five folds, using four folds as the training set and the remaining fold as the internal validation set, and repeating the above process five times. The models were compared on the test set to evaluate the model performance. Five predictive models were constructed, including (eXtreme Gradient Boosting) XGBoost, Logistic Regression, Light Gradient Boosting Machine (LightGBM), Random Forest and (Adaptive Boosting) AdaBoost. To further enhance the performance and usability of the model, we selected the top four features from the best-performing model. This ensures that the models are built on the most influential and relevant features.

Shapley additive explanation (SHAP) analysis was used to demonstrate the contribution of features in the selected model. Model performance was assessed using the receiver operating characteristics (ROC) curve, calibration curve, and decision curve analysis (DCA).

Statistical analysis

Continuous variables were presented as either Mean ± SD or median (IQR). The student's t-test or Mann–Whitney U test was applied depending on whether the variables were normally distributed. Categorical variables were compared using the chi-square test. A two-sided *P*-value <0.05 was considered statistically significant. Univariate and multivariate logistic regression analyses were performed to identify risk factors for sepsis in patients with HIV. We assessed the outcomes of the diagnostic test using sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), ROC, and AUC. Additionally, we employed PCT, and CRP as comparative diagnostic markers alongside MDW. All statistical analyses and machine learning model construction were performed using the Beckman Coulter DxAI platform (https://www.xsmartanalysis.com/beckman/login/). Given that MDW's performance might be influenced by sample selection and pathological conditions, and based on statistical considerations ($\alpha = 0.05$, $\beta = 0.8$, error margin = 0.08), the anticipated sensitivity of MDW in diagnosing sepsis is 75%, with specificity at 70%. Therefore, the required sample size for this diagnostic trial is 488 cases.

Results

Patients characteristics

The study flow diagram is illustrated in Figure 1. Out of 602 initially screened individuals, 488 participants were included in the study after applying exclusion criteria and removing duplicates, meeting the predetermined sample size. Baseline characteristics of these subjects are detailed in Table 1. Using Sepsis-3 as the gold standard, participants were divided into the sepsis group (n = 90) and the control group (n = 398). The overall mean age was 40.5 years, with the sepsis group being older (45.3 years) compared to the control group (39.6 years). The study population, including both groups, was predominantly male (426, 87.3%), and there was no significant gender difference between the groups. $CD4^+$ T cell count and $CD4^+$ T cell/$CD8^+$ T cell ratio were lower in the sepsis group compared to the control group (139.22cell/μL / vs 37.06 cell/μL, 0.22 vs 0.11, $P < 0.001$), whereas HIV viral load was higher in the sepsis group (207,000 copy/mL vs 622 copy/mL, $P < 0.001$). The MDW was significantly higher in the sepsis group compared to the control group (21.68 vs 28.99, $P < 0.001$), and similar trends were observed for CRP and PCT (40.89 mg/L vs 3.53 mg/L, 0.38 ng/mL vs 0.05 ng/mL, $P < 0.001$). Among the complications, pulmonary infections were the most prevalent, followed by syphilis, lymphoma, and non-tuberculous mycobacteria.

Efficacy of MDW for diagnosing sepsis and comparison with PCT and CRP in patients with HIV

Figure 2A shows comparison of median MDW values between the control group and the sepsis group (21.68 vs 28.99, $P < 0.001$). The ROC curve for MDW in diagnosing sepsis is shown in Figure 2B, with an area under the curve (AUC) of 0.82(95% CI: 0.77–0.85). We selected the cutoff value that maximizes the Youden index, with the optimal cutoff for MDW in diagnosing sepsis calculated to be 25.25. The sensitivity and specificity of MDW in diagnosing sepsis were 0.82 (95% CI: 0.74–0.90) and 0.76 (95% CI: 0.72–0.80), respectively, with a Kappa value of 0.445. Furthermore, we compared the diagnostic performance of MDW with PCT and CRP. The diagnostic ability of MDW was similar to that of PCT (AUC: 0.82 [95% CI: 0.76–0.86]) and superior to CRP alone (AUC: 0.78 [95% CI: 0.72–0.83]). The combined use of the three indicators further improved the diagnostic performance (AUC: 0.83 [95% CI: 0.76–0.87]). Supplementary Table 1 presents the evaluation metrics for diagnosing sepsis in HIV patients using the three diagnostic methods, demonstrating that MDW has higher accuracy, specificity, negative predictive value, and Kappa value compared to PCT and CRP. Subsequently, Supplementary Table 2 shows multivariate analysis to identify predictive factors for the development of sepsis in patients with HIV and found that HIV non-viremia was one of the risk factors. Therefore, we compared the mean MDW values between

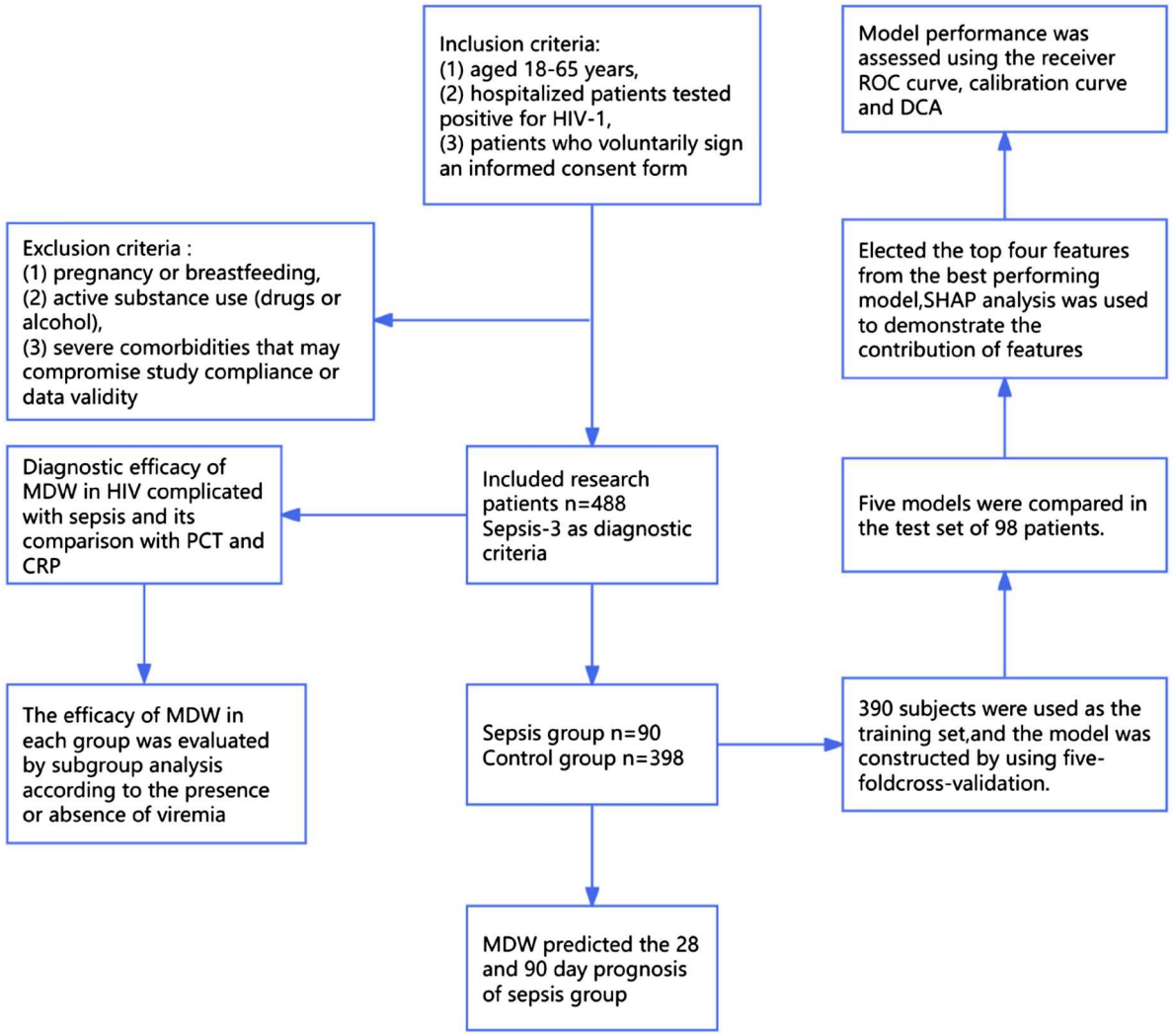

Figure 1. Flowchart of study population.

viremic sepsis group, non-viremic sepsis group, viremic control group and non-viremic control group (29.5 vs 30.7 vs 24.8 vs 21.8) in Figure 2C. Furthermore, we analyzed the diagnostic performance of MDW, PCT, CRP and their combination for diagnosing sepsis in the HIV viremia subgroup in Figure 2D, with AUC values of 0.76 (95% CI: 0.68–0.84), 0.79 (95% CI: 0.72–0.85), and 0.74 (95% CI: 0.66–0.82), respectively. Figure 2E presents the ROC curves for MDW, PCT, CRP, and their combined assessment in the HIV non-viremic group for the diagnosis of sepsis. The corresponding AUC values are 0.83(95% CI: 0.72–0.93), 0.87(95% CI: 0.78–0.96), 0.82(95% CI: 0.71–0.94), and 0.82(95% CI: 0.70–0.94), respectively.

Variable selection using supervised machine learning algorithms

A total of 21 variables with significant statistical differences between the two study groups were included in the supervised machine learning algorithms, such as serum albumin, hemoglobin, MDW, and PCT. Spearman correlation analysis was conducted to assess multicollinearity among the variables. The training set, consisting of 390 individuals, utilized five-fold cross-validation to construct the models, while a separate set of 98 individuals was used to evaluate model performance. Five predictive models were developed, including XGBoost, Logistic regression, Light Gradient Boosting Machine, Random Forest, and AdaBoost.

Supplementary Table 3 presents the evaluation metrics for the five models, including AUC, accuracy, sensitivity, specificity, PPV, NPV, and FI score. Figure 3A depicts the clinical decision curves for the five predictive models. The Random Forest model demonstrated a higher net benefit within the threshold ranges of 0–0.2 and 0.6–0.9. Figure 3B shows the calibration curves for the five models, with the Random Forest model's calibration curve closely aligning with the ideal line, achieving a Brier score of 0.125, indicating higher predictive accuracy. Figure 3C illustrates the ROC curves for the five models, with the Random Forest model attaining the highest AUC of 0.86. Consequently, we selected the Random Forest model to construct the final model.

Table 1. Demographics and clinical data of the study population stratified in two groups.

Variable	Total(n = 488)	Control group (n = 398)	Sepsis group(n = 90)	*P*
Age, Median [IQR]	40.5 (32.5, 53.0)	39.5(32.0, 51.5)	45.0(34.5, 56.5)	0.01
Gender, n(%) Female	62(12.71)	47(11.81)	15(16.67)	0.21
Male	426(87.30)	351(88.19)	75(83.33)	
MDW, Median [IQR]	22.67 (20.02, 27.00)	21.68(19.33, 25.22)	28.990(26.09, 33.13)	<0.001
CRP, Median [IQR]	5.01 (1.31, 40.89)	3.53(0.86, 23.30)	40.890(12.90, 96.25)	<0.001
PCT, Median [IQR]	0.08 (0.04, 0.26)	0.05(0.03, 0.13)	0.380(0.12, 0.91)	<0.001
CD4T cell count, Median [IQR]	110.92 (31.29, 266.46)	139.22(44.64, 292.54)	37.060(11.44, 96.28)	<0.001
CD4/CD8, Median [IQR]	0.20 (0.08, 0.44)	0.22(0.10, 0.49)	0.110(0.06, 0.21)	<0.001
HIV load, Median [IQR]	18500(20, 348750)	662(20, 269000)	207000(2830, 1155000)	<0.001
HIV virological inhibition, n (%)	100/315(31.75)	7/65(10.77)	93/250(37.20)	<0.001
with ART, n(%)	374(76.64)	318(79.90)	56(62.22)	<0.001
Hemoglobin, median [IQR]	122.00(98.00, 141.00)	126.00(106.00, 143.00)	87.00(72.00, 114.00)	<0.001
Platelet, median [IQR]	204.00(144.00, 269.00)	214.00(169.00, 277.00)	122.00(70.00, 203.00)	<0.001
Leucocyte, median [IQR]	5.07(3.65, 6.99)	5.13(3.73, 6.89)	4.54(3.09, 7.53)	0.23
Neutrophil, median [IQR]	3.09(2.01, 4.80)	3.01(2.03, 4.59)	3.33(1.77, 6.18)	0.25
Lymphocyte, median [IQR]	1.10(0.67, 1.72)	1.24(0.76, 1.80)	0.68(0.41, 1.03)	<0.001
Monocyte, median [IQR]	0.42(0.30, 0.57)	0.43(0.32, 0.59)	0.36(0.21, 0.53)	<0.001
Total bilirubin, median [IQR]	8.90(6.11, 13.20)	8.70(6.00, 12.20)	10.80(6.80, 17.10)	0.01
ALT, median [IQR]	22.00(14.00, 40.00)	21.00(13.00, 40.00)	27.00(14.00, 44.00)	0.33
AST, median [IQR]	22.00(17.00, 36.00)	21.00(16.00, 31.00)	32.00(21.00, 55.00)	<0.001
Albumin, median [IQR]	38.20(32.70, 42.30)	39.70(35.70, 42.86)	30.00(25.10, 34.30)	<0.001
Creatinine clearance rate, median [IQR]	111.65(92.53, 135.10)	112.09(94.11, 133.22)	110.93(86.88, 145.55)	0.98
Fasting blood glucose, median [IQR]	6.01(5.19, 7.26)	6.01(5.19, 7.24)	6.09(5.14, 7.32)	0.78
Blood lactic acid, median [IQR]	1.26(0.93, 1.74)	1.20(0.90, 1.70)	1.39(1.00, 1.80)	0.15
Complication, n (%)				
lung infection	91(18.65)	66(16.58)	25(27.78)	0.01
syphilis	61(12.50)	52(13.06)	9(10.00)	0.43
lymphoma	59(12.09)	48(12.06)	11(12.22)	0.97
NTM	54(11.07)	43(10.80)	11(12.22)	0.70
cryptococcosis	44(9.02)	34(8.54)	10(11.11)	0.44
tuberculosis	41(8.40)	36(9.04)	5(5.56)	0.35
PCP	36(7.38)	21(5.27)	15(16.67)	<0.001
diabetes	29(5.94)	23(5.78)	6(6.67)	0.75
hypertension	25(5.12)	18(4.52)	7(7.78)	0.21
hepatitis B	21(4.30)	18(4.52)	3(3.33)	0.62
Talaromyces marneffei	16(3.28)	10(2.51)	6(6.67)	0.05
Kaposi sarcoma	15(3.07)	9(2.26)	6(6.67)	0.03

MDW, monocyte distribution width; PCT, procalcitonin; CRP, C-reactive protein; ART, antiretroviral therapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NTM, non-tuberculous mycobacteria; PCP, pneumocystis pneumonia.

Constructed model using selected variables enhances diagnostic performance for sepsis in patients with HIV

From the selected Random Forest model, we identified the top four variables to ensure the model was based on the most influential and relevant predictors. Supplementary Figure 1A and B illustrate the ROC curves for this model on the training and test sets, with AUC of 0.87 and 0.93, respectively. The model achieved a sensitivity of 1.00 and specificity of 0.732 on the test sets. Supplementary Figure 1C shows the clinical decision curve of the model on the test set, indicating a high net benefit. Supplementary Figure 1D presents the calibration curve of the model, with a Brier score of 0.072, indicating high predictive accuracy.

Figure 4A illustrates the distribution of SHAP values for the model. It is evident that MDW contributes significantly to positive predictions in most samples. Conversely, platelet SHAP values are predominantly negative, indicating a significant impact on negative predictions in most cases. Through SHAP value analysis, we can better understand the model's decision-making process, thereby enhancing the model's transparency and reliability. Figure 4B presents the mean SHAP values for various features within the model. The mean SHAP value for MDW exceeds 0.06, indicating a substantial contribution to the model's predictive outcome, whereas the mean SHAP value for hemoglobin is approximately 0.03, suggesting a lesser impact on the predictive outcome. These findings assist in identifying the most important features in the model.

A webpage tool is displayed online through the Beckman Coulter DxAI platform to facilitate the clinical use of the model (http://www.xsmartanalysis.com/model/list/predict/model/html?mid=9699&symbol=1pp169995hv026Nr33Ii) [4]. After inputting the necessary parameters, the patient could be discriminated as sepsis or non-sepsis with predicted probability.

Predictive utility of MDW for 28-day and 90-day prognosis of sepsis in patients with HIV

Accurate prognostic prediction for the occurrence of sepsis in patients with HIV can facilitate targeted treatment approaches. In this context, we investigated the capability of MDW to predict the 28-day and 90-day outcomes in 90 patients with HIV with sepsis.

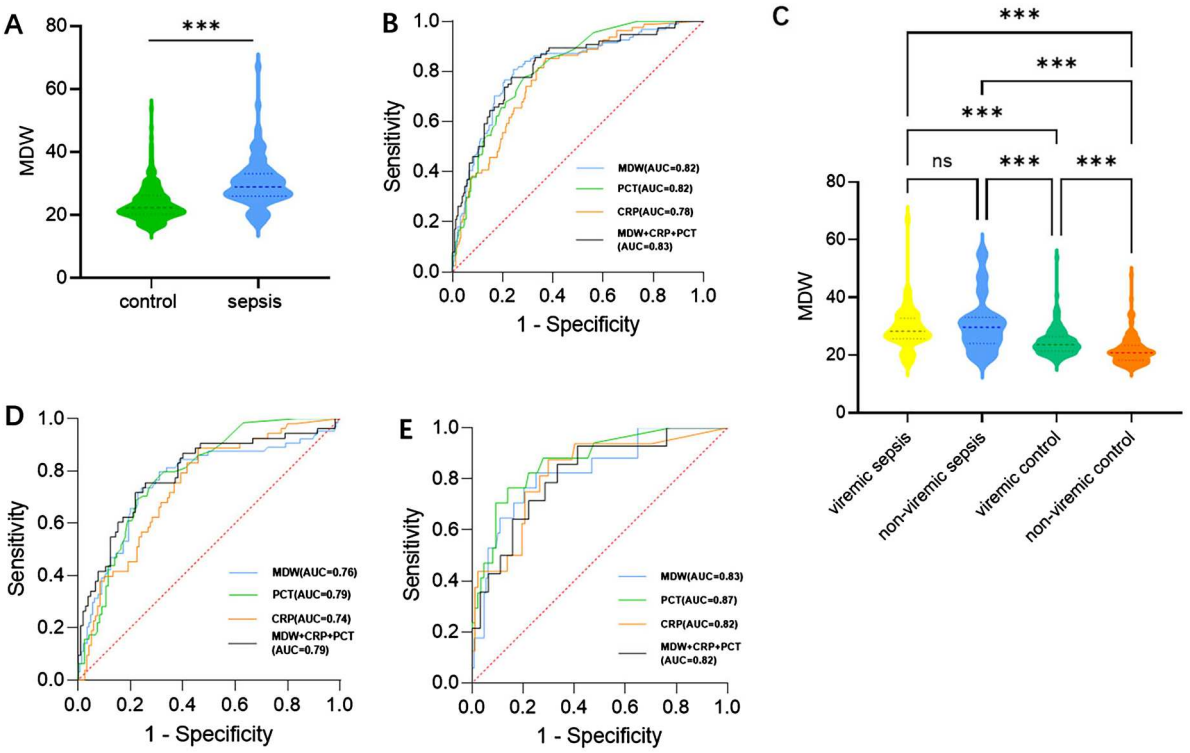

Figure 2. (A) Comparison of median MDW values between the control group and the sepsis group (21.7 vs 29.0, $P < 0.001$). (B) ROC curve analysis of MDW, PCT, CRP, and their combination for the diagnosis of sepsis in patients with HIV. (C) Comparison of median MDW values among the viremic sepsis group, non-viremic sepsis group, viremic control group and non-viremic control group (29.5 vs 30.7 vs 24.8 vs 21.8). Pairwise comparisons among the groups revealed significant differences in all comparisons except between viremic sepsis group and non-viremic sepsis group. (D) Subgroup analysis: ROC curve for the diagnostic performance of MDW, PCT, CRP, and their combination in HIV viremia patients for sepsis diagnosis.(E) Subgroup analysis: ROC curve for the diagnostic performance of MDW, PCT, CRP, and their combination in HIV non-viremia patients for sepsis diagnosis.

For the 28-day prognosis, AUROC was 0.68(95%CI: 0.51–0.84), with a sensitivity of 0.89 and specificity of 0.53. For the 90-day prognosis, the AUROC was 0.64(95%CI: 0.47–0.80), with a sensitivity of 0.87 and a specificity of 0.51. These findings underscore the potential of MDW as a predictive marker for short and medium-term outcomes in patients with HIV (Supplementary Figure 2).

Discussion

In this study, we evaluated the diagnostic efficacy of MDW for detecting sepsis in patients with HIV, establishing a critical threshold of 25.25. We compared its performance with that of PCT and CRP. It was also found that MDW holds certain value in diagnosing sepsis in HIV viremic and non-viremic patients.

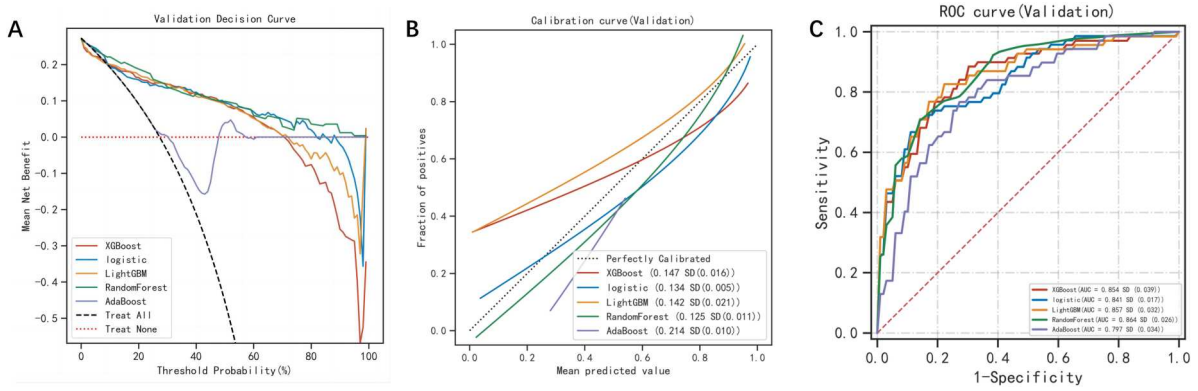

Figure 3. Evaluation of diagnostic efficacy of five models of sepsis in patients with HIV. **(A)** The clinical decision curves for the five predictive models. The random forest model demonstrated a higher net benefit within the threshold ranges of 0–0.2 and 0.6–0.9. **(B)** The calibration curves for the five models, with the Random Forest model's calibration curve closely aligning with the ideal line, achieving a Brier score of 0.125. **(C)**The ROC curves for the five models, with the Random Forest model attaining the highest AUC of 0.86.

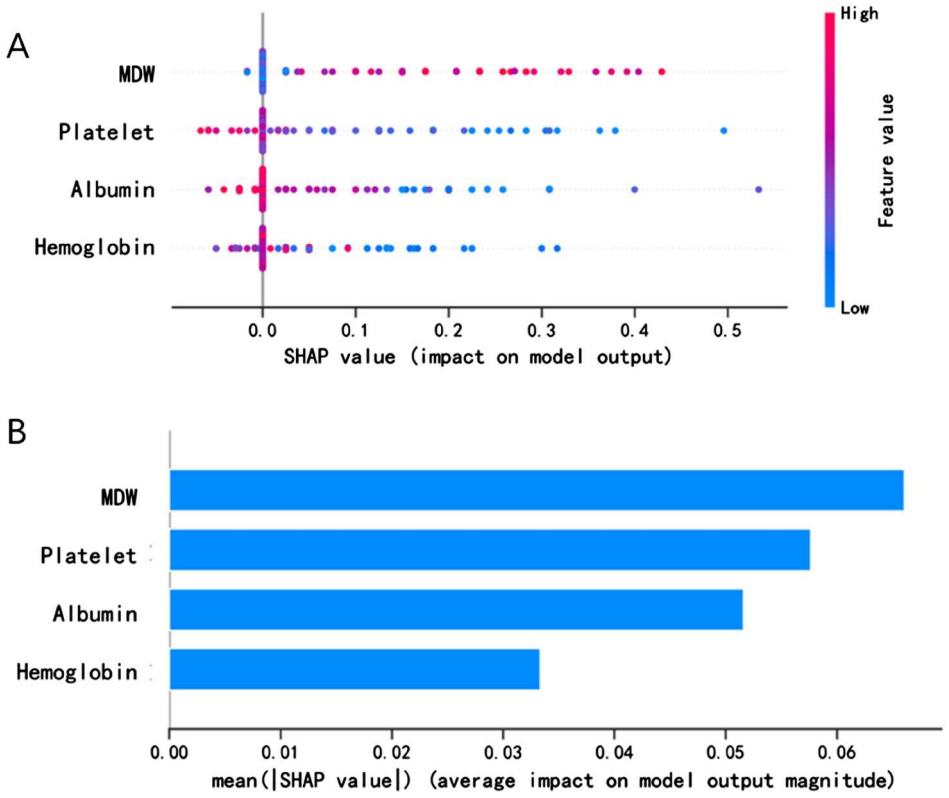

Figure 4. Shapley additive explanation (SHAP) analysis was used to demonstrate the contribution of features in the selected model. **(A)** The distribution of SHAP values for the model. It is evident that MDW contributes significantly to positive predictions in most samples. **(B)** The mean SHAP values for various features within the model. The mean SHAP value for MDW exceeds 0.06, indicating a substantial contribution to the model's predictive outcome.

Subsequently, multiple ML models were employed to select four variables, and we developed and validated an MDW-based model for diagnosing sepsis in patients with HIV. The diagnostic model demonstrated accuracy in both the training and validation cohorts. Additionally, in terms of prognosis, MDW showed limited predictive power for 28-day and 90-day outcomes.

Currently, there is no gold standard for the diagnosis of sepsis [4–6]. The most widely accepted diagnostic method utilizes the Sepsis-3 criteria, which are recognized for their high diagnostic efficacy [7]. However, this standard has several limitations, including a complex assessment process and lengthy time requirements [8]. MDW has emerged as a promising biomarker for the diagnosis of sepsis [13, 24]. Previous studies have demonstrated its effective diagnostic performance [25]. For instance, research by Pierre H et al. [26] found that MDW had a diagnostic efficacy of 0.82. Notably, most of these studies excluded patients with HIV, despite the high mortality rates associated with HIV [27]. Thus, accurate diagnosis of sepsis in patients with HIV is crucial, highlighting the potential importance of MDW in this context.

In our study, we observed that the threshold value for MDW in sepsis occurrence among patients with HIV is higher compared to uninfected individuals. Moreover, in the control group, patients with HIV viremia exhibited higher MDW values compared to those in the non-viremia group. A potential explanation for this could be the critical role monocytes play in HIV infection, such as antigen presentation [28]. In patients with HIV, monocytes and macrophages undergoing persistent activation [20]. This may lead to morphological changes, which could influence MDW values [29]. A similar phenomenon has been observed in the context of COVID-19 infection and Hepatitis B virus infection [17, 30, 31]. In these diseases, the cutoff value of MDW is elevated compared to that in the general patient population [32], and it can serve as a valuable biomarker for diagnosing the severity of the disease [17]. Previous studies have demonstrated that the diagnostic cutoff value of MDW for sepsis is determined based on bacterial infections, with MDW values being higher in cases of viral infections [18]. These findings highlight that the MDW threshold values applicable to non-HIV-infected individuals should not be used to diagnose sepsis in patients with HIV. Clinicians should be aware of the HIV status of patients when using this biomarker, which holds significant implications for clinical diagnostics.

As ML continues to evolve, clinicians are increasingly able to transform extensive clinical data into predictive models to enhance diagnostic capabilities for

diseases [21]. For example, Zheng, Y, et al. developed a diagnostic model for sepsis-induced acute lung injury, achieving an AUC of 0.83, demonstrating the potential of such approaches [33]. However, these studies typically do not include patients with HIV, failing to meet the clinical diagnostic needs for sepsis in this population. Compared to traditional methods, ML algorithms have shown superior performance in disease diagnosis [34]. Consequently, we have developed and validated a diagnostic model specifically for sepsis in patients with HIV. This model includes the previously discussed MDW along with other readily available clinical hematological parameters, achieving an AUC of 0.93. This signifies a substantial improvement in the diagnostic accuracy for sepsis among patients with HIV.

Our study identified four clinical indicators for model construction, namely MDW, platelets, albumin, and hemoglobin. The role of MDW in sepsis has been previously discussed. In sepsis diagnostic models for non-HIV-infected populations, the latter three indicators have been included in various models due to their significant roles in the pathogenesis of sepsis [35]. Notably, platelet count is one of the criteria in the Sepsis-3 scoring system [36]. While many models incorporate white blood cell count as an indicator, it was not included in our model, presenting a potential area for further investigation [35, 37].

The study has several limitations that merit consideration. Firstly, in our study design, MDW was measured within 3 h rather than 2 h, which may result in some MDW values being elevated [38, 39]. Additionally, we employed the Sepsis-3 criteria and did not compare it with other standards, such as Sepsis-2 [36]. Secondly, the data for the model were sourced from a single center and primarily developed using data from patients in China. This necessitates further validation in multicenter studies and across diverse ethnic groups to ensure its generalizability. Thirdly, as most of the study data were derived from clinical records, there was an incidence of missing data due to some patients not undergoing certain tests. Finally, the study shows that circulating histones can cause changes in MDW and also increase inflammatory cytokines [40]. However, our study did not further explore the relationship between MDW and immune activation parameters in HIV-infected individuals, such as CD4 HLA-DR/CD38. These limitations highlight areas for improvement in future research to enhance the robustness and applicability of the findings.

MDW was an auxiliary diagnostic biomarker for sepsis in patients with HIV with reliable sensitivity and specificity. In combination MDW with other common laboratory biomarkers, a diagnostic model can be established to further improve the diagnostic efficiency of sepsis.

Abbreviations

ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under curve
CRF	case report form
CRP	C-reactive protein
DCA	decision curve analysis
MDW	monocyte distribution width
ML	machine learning
NPV	negative predictive value
NTM	non-tuberculous mycobacteria
PCP	pneumocystis pneumonia
PCT	Procalcitonin
PPV	positive predictive value
ROC	receiver operating characteristic
SHAP	Shapley additive explanation
SOFA	sequential organ failure assessment

Disclosure statement

LQ, XLW, and YWT are employees of Danaher Beckman-Coulter, the commercial manufacturer of the K2EDTA tubes and the hematology analyzer DxH900 system. The remaining authors declare no competing interests.

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