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ORIGINAL RESEARCH

Early Elevation of Monocytic-to-Polymorphonuclear Myeloid-Derived Suppressor Cells Ratio in Critical Illness is Associated with Favorable Clinical Outcomes

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Background: Myeloid-derived suppressor cells (MDSCs), comprising polymorphonuclear (PMN-MDSCs) and monocytic subsets (M-MDSCs), are immunosuppressive immature myeloid cells implicated in disease progression and prognosis across multiple pathologies.

Purpose: To investigate the clinical significance of early MDSCs subset expansion in critical illness and identify novel prognostic biomarkers for risk stratification.

Patients and Methods: This prospective study enrolled 85 critically ill adults (APACHE II ≥15), stratified into survivors (n=47) and non-survivors (n=38). MDSCs subsets were quantified via flow cytometry. Concurrent measurements included lactate, IL-6, CRP, lymphocyte subsets, and Tregs. Primary outcomes were 28-day all-cause mortality and secondary infection rates.

Results: Survivors exhibited significantly higher M-MDSCs% (median [IQR]: 4.824 [1.863–9.776] vs 2.503 [1.480–5.224], P<0.05) and elevated M-MDSCs/PMN-MDSCs ratios (122.166 [34.220–307.500] vs 28.324 [5.042–88.128], P<0.01). Patients with M-MDSCs/PMN-MDSCs ratios ≥85.765 demonstrated markedly lower mortality (23.08% vs 59.19%; hazard ratio [HR] = 3.530, 95% confidence interval [CI]: 1.668–7.467, P<0.001), with the low-ratio group exhibiting a 2.56-fold higher mortality risk. A combined stratification model (M-MDSCs/PMN-MDSCs + APACHE II score) revealed a 7.48-fold increase in mortality in the low-ratio/high-APACHE II subgroup compared to the high-ratio/low-APACHE II subgroup (86.36% vs 11.54%, P<0.001).

Conclusion: Elevated levels of M-MDSCs in the early stages of critical illness may exert protective effects. The ratio of M-MDSCs/PMN-MDSCs demonstrates predictive value for 28-day mortality, positioning it as a potential biomarker for prognostic assessment, but further multicenter studies are still needed to validate it.

Keywords: myeloid-derived suppressor cells, critically ill, prognosis

Introduction

The initial discovery of immune suppressive cells originating from myeloid precursors dates back to the 1980s, when researchers investigating cancer patients identified a population of functionally suppressive myeloid cells.[1,2] These cells were provisionally termed Natural Suppressor Cells (NSCs) and Immature Myeloid Cells (IMCs) based on their developmental origin and immunosuppressive characteristics. Following two decades of characterization efforts, the scientific community formally adopted the nomenclature "Myeloid-Derived Suppressor Cells" (MDSCs) in 2007 to standardize research terminology.[3]

MDSCs are currently classified into two principal subtypes based on morphological and phenotypic criteria: polymorphonuclear MDSCs (PMN-MDSCs) resembling granulocytes, and monocytic MDSCs (M-MDSCs) sharing features with monocytes.[4] Immunophenotyping reveals distinct surface marker profiles: human PMN-MDSCs are characterized by $CD33^{+}CD11b^{+}CD15^{+}HLA\text{-}DR^{low}$ expression, while M-MDSCs exhibit $CD33^{+}CD11b^{+}CD14^{+}HLA\text{-}DR^{low}$ markers.[5]

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Additionally, researchers have identified a minor population (<5% of total MDSCs) of developmentally primitive cells designated as early-stage MDSCs (e-MDSCs).[6] These precursor cells emerge during initial disease progression and display a unique $CD33^{+}CD11b^{+}HLA\text{-}DR^{low}CD14^{-}CD15^{-}$ profile, lacking both granulocytic and monocytic differentiation markers.[7]

Myeloid-derived suppressor cells (MDSCs) represent a heterogeneous population of immunosuppressive cells that undergo pathological expansion during chronic inflammatory conditions and carcinogenesis. These cells exert multi-faceted pro-tumorigenic effects through immune evasion mechanisms, tumor angiogenesis promotion, and direct support of malignant progression.[8] Emerging evidence indicates that MDSCs also demonstrate significant expansion in acute inflammatory pathologies, including trauma, burn injuries, and sepsis.[9,10]

Critically ill patients often manifest a spectrum of immune dysregulation ranging from partial functional impairment to complete immune paralysis. This immunological disturbance can lead to cellular damage, progressive organ dysfunction, and ultimately multi-system failure. The co-occurrence of hyperinflammation and immunosuppression - a hallmark of critical illness - constitutes a pathophysiological paradox wherein both pro-inflammatory and anti-inflammatory pathways are simultaneously activated. Although these dual processes may temporally overlap, their etiological drivers, molecular mechanisms, and clinical trajectories demonstrate distinct characteristics.

Notably, patients with sepsis, major trauma, or severe infections typically exhibit concurrent elevation of inflammatory mediators and immunosuppressive markers. A pivotal clinical study revealed that trauma patients demonstrate three characteristic immunological alterations within hours post-injury: 1) significant elevation of pro-inflammatory cytokines (IL-6) and chemokines (IL-8), 2) paradoxical upregulation of the anti-inflammatory cytokine IL-10, and 3) marked downregulation of HLA-DR expression on circulating monocytes.[11] This rapidly developing immunosuppressive state, occurring synchronously with systemic inflammation, underscores the complexity of immune homeostasis disruption in critical care settings.

Despite well-established understanding of myeloid-derived suppressor cells (MDSCs) in tumor immunology, critical knowledge gaps persist regarding the functional characteristics of different MDSCs subsets during early critical illness. The temporal dynamics of PMN-MDSCs and M-MDSCs expansion, their molecular mechanisms in immune regulation, and ultimate prognostic value remain underinvestigated. To address these unresolved issues, we conducted this study aiming to elucidate the clinical significance of early MDSCs expansion in critically ill patients, thereby providing evidence for clinical decision-making and optimizing prognostic evaluation.

Methods

Study Design and Setting

This prospective observational cohort study was conducted at the intensive care unit (ICU) of Hebei General Hospital, a tertiary academic medical center. The protocol was prospectively registered with the Chinese Clinical Trial Registry (Registration ID: ChiCTR2300079024) and received ethical approval from the Institutional Review Board of Hebei General Hospital (Ethical Approval Code: 2023–410). The study adhered to the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal representatives prior to study enrollment.

Study Population

Study Population Between March 2024 and July 2024, consecutively admitted ICU patients meeting predefined criteria were stratified based on 28-day survival outcomes into survivors and non-survivors (Figure 1). Inclusion criteria required: 1) age ≥18 years; 2) APACHE II score ≥15; and 3) informed consent. Exclusion criteria comprised: 1) pregnancy; 2) active malignancy; 3) organ transplant recipients; 4) HIV-positive status; and 5) prior use of corticosteroids or immunosuppressants.

Data Collection and Processing

Peripheral blood samples were collected in EDTA-anticoagulated tubes within 48 hours of ICU admission. A standardized flow cytometry protocol utilizing a BD Biosciences FACSCanto II flow cytometer with fluorescence-labeled antibodies was employed to quantify myeloid-derived suppressor cells (MDSCs) and their subsets: polymorphonuclear MDSCs and

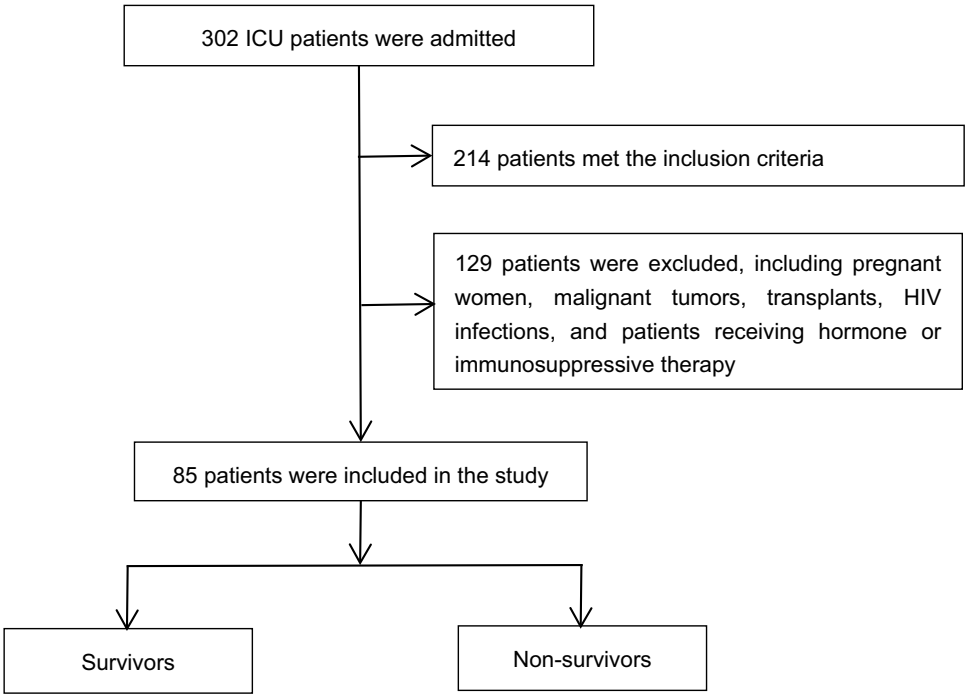

Figure 1 Patients enrolled in our study.

monocytic MDSCs, as well as lymphocyte subsets and regulatory T cells (Tregs). Concurrent laboratory analyses included complete blood count, serum lactate, interleukin-6 (IL-6), and C-reactive protein (CRP) measurements. Patients were prospectively followed for 28 days to monitor secondary infections, defined as new-onset microbiologically confirmed infections occurring >48 hours after hospital admission. The primary endpoints included all-cause mortality and nosocomial infection rates.

Flow Cytometric Analysis of MDSCs

Peripheral Blood Mononuclear Cell (PBMC) Isolation

1. Density gradient preparation: A Ficoll-Paque density gradient was established by layering 1.5 mL of Ficoll-Paque™ PLUS (GE Healthcare) in a 15 mL conical tube.
2. Sample preparation: Whole blood was diluted 1:1 with phosphate-buffered saline (PBS) in a separate tube.
3. Gradient centrifugation: The diluted blood sample was carefully layered onto the Ficoll gradient and centrifuged at 400 ×g for 20 min at 20°C with brake disengaged.
4. PBMC collection: The mononuclear cell layer at the plasma-Ficoll interface was aspirated using a sterile Pasteur pipette.
5. Cell washing: PBMCs were washed twice with PBS (2 mL per wash) through centrifugation at 300 ×g for 5 min, followed by resuspension in 200 μL PBS.

Immunostaining Protocol

The following fluorescently conjugated anti-human monoclonal antibodies were titrated in a polystyrene tube:CD15-FITC (clone H198), CD11b-PE (clone ICRF44), CD45-PerCP (clone 2D1), CD33-PE-Cy7 (clone WM55), HLA-DR-APC (clone LN3), CD14-APC-Cy7 (clone 61D3).

Staining Procedure

100 μL PBMC suspension (1×10^6 cells) was added to the antibody mixture. Vortexed gently and incubated protected from light for 15 min at 4°C. Washed with 2 mL PBS (300 ×g, 5 min). Resuspended in 500 μL PBS for acquisition.

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Flow Cytometric Acquisition and Analysis

Samples were analyzed within 2 hours using a BD FACSCanto II flow cytometer (BD Biosciences) with FACSDiva™ software (v8.0.1). The gating strategy (Figure 2) was established as follows:

M-MDSCs: $CD45^{+}CD33^{+}CD11b^{+}CD14^{+}CD15^{-}HLA\text{-}DR^{-}$

PMN-MDSCs: $CD45^{+}CD33^{+}CD11b^{+}CD14^{-}CD15^{+}HLA\text{-}DR^{-}$

$$M-MDSCs\% = \frac{M-MDSCs\ cell\ count}{CD45+\ cell\ count} \times 100\%$$

$$PMN-MDSCs\% = \frac{PMN-MDSCs\ cell\ count}{CD45+\ cell\ count} x100\%$$

Flow Cytometric Analysis of Lymphocyte Subsets and Regulatory T Cells

Sample Preprocessing

Fresh peripheral blood was gently mixed by inversion, and 30–50 μL of the blood was aliquoted and incubated with fluorescence-conjugated antibodies in a light-protected environment for 15 minutes. Hemolysin was then added to lyse red blood cells, followed by washing steps to clarify the cells before loading onto the flow cytometer for analysis.

Gating Strategy

Based on the principles of flow cytometry, the primary cell population was gated using forward scatter (FSC, reflecting relative cell size) and side scatter (SSC, indicating internal structural complexity). Subsequently, lymphocytes were further gated using CD45 expression combined with SSC. Cell subsets were then identified based on surface-specific antigen expression:

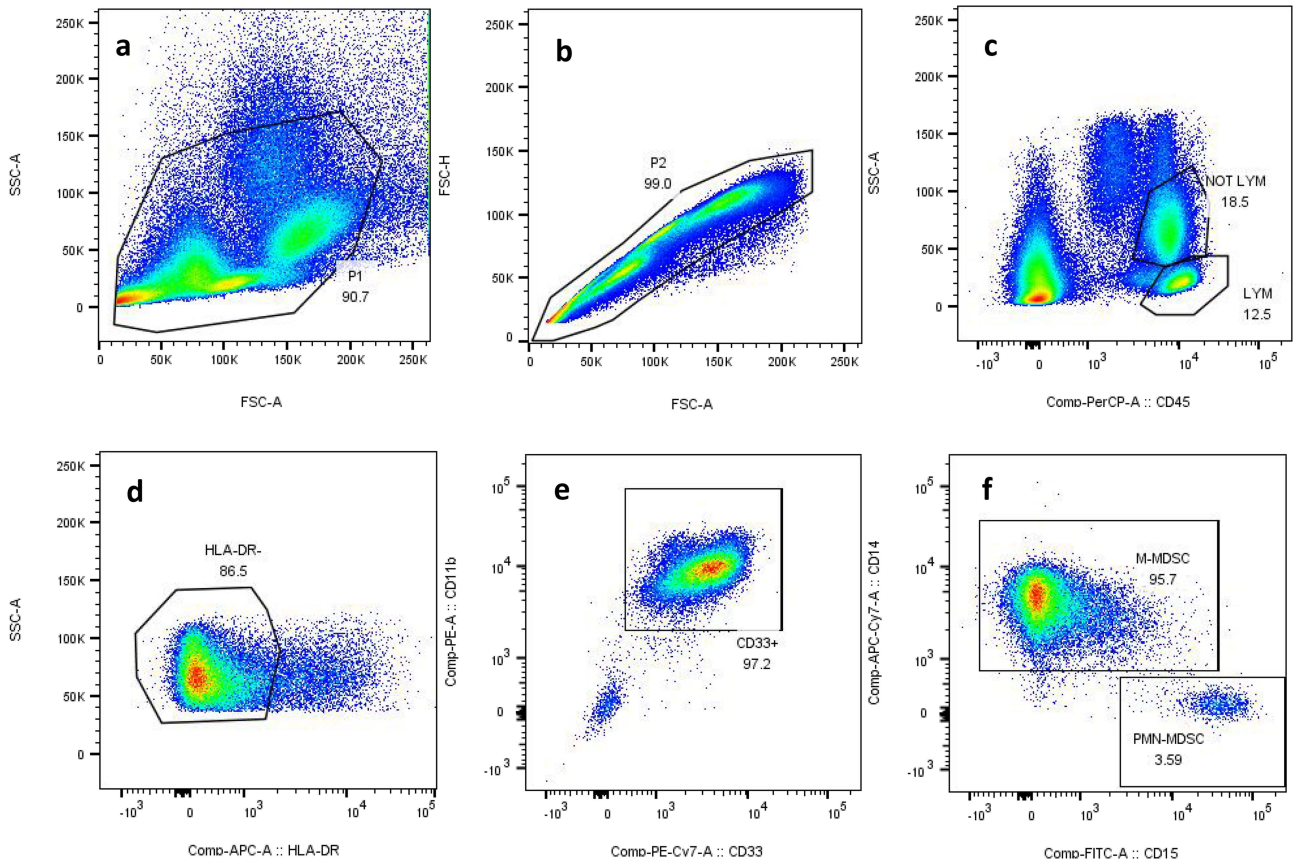

Figure 2 Panels (**a**–**f**) illustrate the gating strategy for identification of MDSCs in critically ill patients.

T lymphocytes: $CD3^+$
Helper/inducer T lymphocytes: $CD3^+CD4^+$
Suppressor/cytotoxic T lymphocytes: $CD3^+CD8^+$
B lymphocytes: $CD3^-CD19^+$
NK lymphocytes: $CD3^-CD16^+CD56^+$
Regulatory T cells (Treg): $CD3^+CD4^+CD25^+CD127^{low/-}$

Testing Methods for Other Indicators

The following indicators were tested by the hospital laboratory.

Blood Analysis (Complete Blood Count, CBC)

Principle: Automated instruments used the electrical impedance method to count red blood cells, white blood cells, and platelets and analyze their morphology.
Method: Anticoagulated whole blood was collected in EDTA tubes and analyzed directly using the instrument.

Interleukin-6 (IL-6)

Principle: The enzyme-linked immunosorbent assay (ELISA) was based on antigen-antibody binding for quantification.
Method:Serum was collected, added to a reagent plate, and results were detected using the instrument.

Lactate

Principle: Lactate oxidase converted lactate into hydrogen peroxide, which was detected via electrochemical sensor methods.
Method: Whole blood samples were added to test strips, and results were rapidly measured using a blood gas analyzer.

C-Reactive Protein (CRP)

Principle: The immunoturbidimetric method detected light signal changes caused by CRP-antibody complex formation.
Method: Serum samples were mixed with reagents, and turbidity was analyzed using an automated instrument.

Statistical Analysis

Statistical analyses were performed using SPSS 25.0 software. Data distribution was initially assessed through normality and homogeneity of variance tests. Normally distributed continuous variables were expressed as mean ± standard deviation (SD) and compared using analysis of variance (ANOVA) for intergroup comparisons, while non-normally distributed quantitative data were summarized as median with interquartile range (IQR) and analyzed via non-parametric methods (eg, Mann–Whitney U-test). Categorical variables were described as frequency (%) and compared using chi-square tests. The predictive performance of indicators was evaluated by receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) quantifying discriminative ability; optimal cutoff values were determined by maximizing Youden's index, and corresponding sensitivity and specificity were calculated. Survival outcomes were presented using Kaplan-Meier curves. A two-tailed p-value < 0.05 was considered statistically significant for all analyses.

Results

Clinical Data

The study enrolled 85 critically ill patients (survivors: n=47; non-survivors: n=38) diagnosed with sepsis, traumatic injury, traumatic brain injury, severe acute pancreatitis, and other critical conditions (Table 1). Compared with non-survivors, survivors exhibited significantly lower median values for age (62.40 ± 14.91 vs 72.63 ± 11.58 years; P = 0.001), Charlson Comorbidity Index (CCI: 5 [IQR 5–8] vs 9 [7–12.27]; P < 0.001), APACHE II score (19 [17–24] vs 26 [23–30.25]; P < 0.001), and inflammatory biomarkers including IL-6 (119.700 [45.300–222.100] vs 205.500 [114.725–368.555] pg/mL; P = 0.015), lactate (2.500 [1.450–3.400] vs 3.350 [2.065–6.155] mmol/L; P = 0.033), and CRP (108.690 [66.440–177.300] vs 165.200 [97.230–221.325] mg/L; P = 0.036). The incidence of secondary infections was markedly reduced in survivors (27.66% [13/47] vs 50% [19/38]; P = 0.035). Although ICU length of stay showed no

Table 1 Characteristics of Patients in the Survivors and Non-Survivors

Characteristic	Non-Survivors	Survivors	χ2/t/Z	p value
Number of patients	38	47	–	–
Gender, male	25	30	0.035	0.851
Age (years)	72.63±11.58	62.40±14.91	−3.466	0.001*
Charlson comorbidity index(CCI)	9(7,12.25)	5(5,8)	−3.777	<0.001*
APACHE II score	26(23,30.25)	19(17,24)	−4.300	<0.001*
IL-6(pg/mL)	205.500(114.725,368.555)	119.700(45.300,222.100)	−2.493	0.015*
Lac(mmol/L)	3.350(2.065,6.155)	2.500(1.450,3.400)	−2.135	0.033*
CRP(mg/L)	165.200(97.230,221.325)	108.690(66.440,177.300)	−2.095	0.036*
WBC($x10^9$/L)	13.465 (8.795,17.283)	12.11 (8.700,18.460)	−0.013	0.989
Neutrophils($x10^9$/L)	12.430 (7.512,15.615)	10.310 (7.220,16.740)	−0.194	0.846
Lymphocyte($x10^9$/L)	0.615 (0.408,1.155)	0.780 (0.630,1.210)	−1.565	0.118
$CD4^+$T cells(pcs/ul)	236.065 (120.250,406.000)	269.000 (154.220,477.000)	−1.445	0.148
$CD8^+$ T cells(pcs/ul)	125.000 (66.818,247.250)	180.000 (127.000,279.000)	−1.569	0.117
B cells(pcs/ul)	101.655 (64.138,230.213)	163.000 (97.000,214.000)	−1.684	0.092
NK cells(pcs/ul)	100.000 (49.645,171.250)	91.000 (61.000,209.000)	−0.296	0.767
Treg cells(%)	6.750 (5.475,10.050)	8.000 (6.100,9.800)	−1.171	0.241
Secondary infections	19(50.00%)	13(27.66%)	4.467	0.035*
Length of ICU stay(days)	7(4,11.25)	8(4,14)	−0.838	0.402
Length of hospital stay(days)	12(5.75,20)	21(14,33)	−4.065	<0.001*

Notes: P<0.05 indicates statistical difference. *Indicating statistical differences.

intergroup difference (median [IQR]: survivors 21 [14,33] vs non-survivors 12 [5.75,20] days; P < 0.001), survivors demonstrated prolonged overall hospitalization duration (P < 0.001).

Differential Expression of M-MDSCs and PMN-MDSCs in Critically Ill Patients

No significant difference was observed in the proportion of PMN-MDSCs between survivors and non-survivors (median [IQR]: 0.049% [0.012–0.141%] vs 0.102% [0.021–0.373%]; P = 0.101). However, M-MDSCs were markedly elevated in survivors compared to non-survivors (4.824% [1.863–9.776%] vs 2.503% [1.480–5.224%]; P = 0.030). Notably, the M-MDSCs/PMN-MDSCs ratio demonstrated a pronounced disparity, with survivors exhibiting a 4.3-fold higher median value than non-survivors (122.166 [34.220–307.500] vs 28.324 [5.042–88.128]; P = 0.001) (Table 2).

Predictive Value of Clinical and Immunological Indicators for 28-Day Mortality in Critically Ill Patients

Receiver operating characteristic (ROC) curve analysis was performed to assess the prognostic utility of age, Charlson Comorbidity Index (CCI), APACHE II score, IL-6, lactate, CRP, M-MDSCs%, and M-MDSCs/PMN-MDSCs ratio for 28-day mortality (Figure 3). The APACHE II score demonstrated the strongest predictive capacity (AUC = 0.772; 95% CI: 0.669–0.875), with an optimal cutoff value of 24.5 yielding 65.8% sensitivity and 78.7% specificity. Notably, the M-MDSCs/PMN-MDSCs ratio showed significant discriminative power (AUC = 0.713; 95% CI: 0.603–0.823), achieving 63.8% sensitivity and 76.3% specificity at a cutoff threshold of 85.765. Other predictors with significant prognostic value included the Charlson Comorbidity Index (CCI; AUC = 0.735) and age (AUC = 0.725), while inflammatory-immune biomarkers demonstrated

Table 2 Levels of MDSCs Subgroups in the Survivors and Non-Survivors

Characteristic	Non-Survivors (n=38)	Survivors (n=47)	t/Z	p value
M-MDSCs(%)	2.503 (1.480, 5.224)	4.824 (1.863, 9.776)	−2.166	0.030*
PMN-MDSCs(%)	0.102 (0.021, 0.373)	0.049 (0.012, 0.141)	−1.640	0.101
M-MDCSs/PMN-MDSCs	28.324 (5.042, 88.128)	122.166 (34.220, 307.500)	−3.318	0.001*

Notes: P<0.05 indicates statistical difference. *Indicating statistical differences.

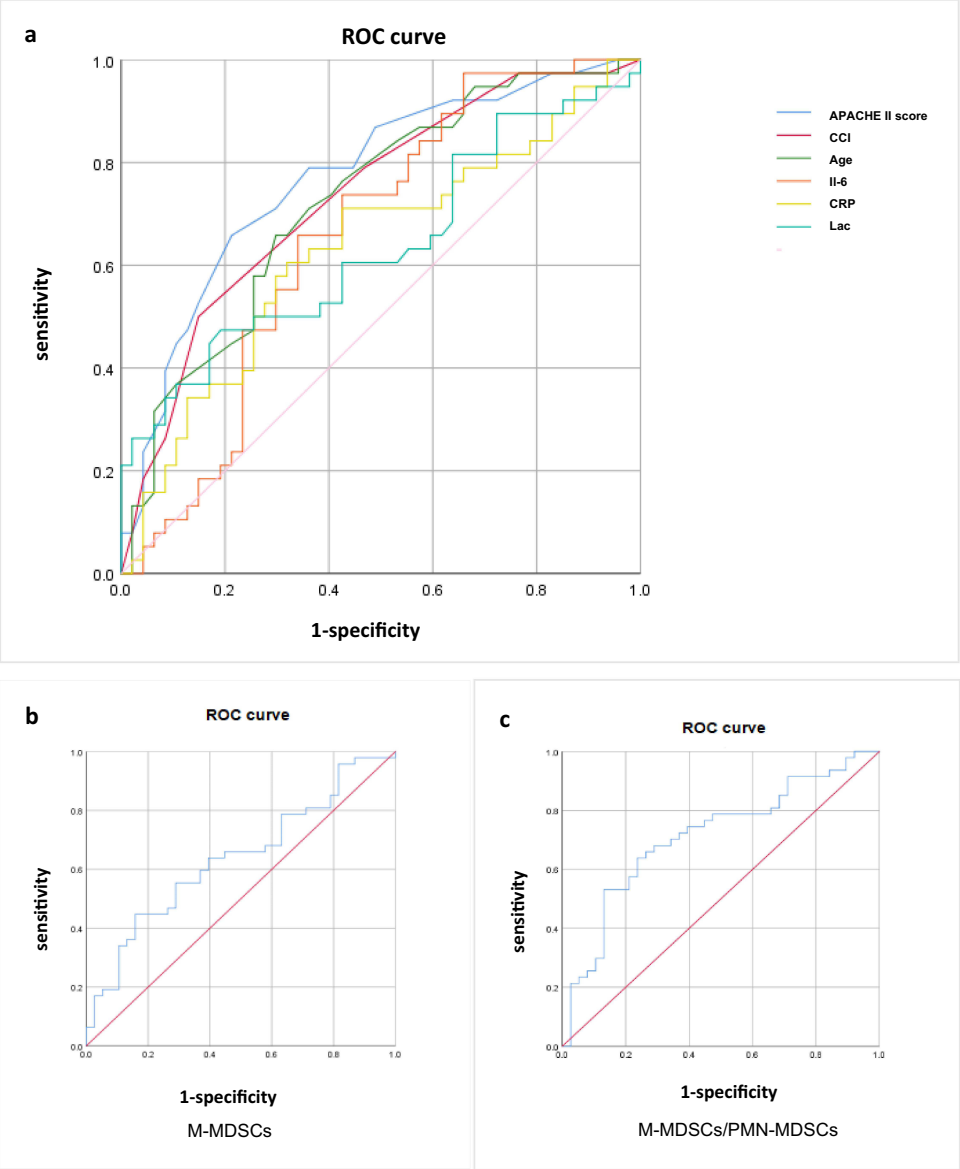

Figure 3 ROC curves for predicting the 28-day mortality rate in critically ill patients using different indicators (**a**) ROC curves of APACHE II score, CCI, age, IL-6, CRP, and Lac; (**b**) ROC curve of M-MDSCs%; (**c**) ROC curve of M-MDSCs/PMN-MDSCs ratio.

moderate predictive performance: interleukin-6 (IL-6; AUC = 0.658), lactate (AUC = 0.635), C-reactive protein (CRP; AUC = 0.633), and monocytic myeloid-derived suppressor cell percentage (M-MDSCs%; AUC = 0.637; sensitivity = 63.8%, specificity = 60.5%).

Prognostic Stratification Based on M-MDSCs/PMN-MDSCs Ratio Cutoff Values in Critically Ill Patients

Critically ill patients were dichotomized into high (≥85.765) and low (<85.765) M-MDSCs/PMN-MDSCs ratio groups using ROC-derived cutoff values. The high-ratio group (n=39) exhibited significantly lower 28-day mortality compared to the low-ratio group (n=46) (23.08% [9/39] vs 59.19% [29/46]; HR=3.53, 95% CI:1.668–7.467; P<0.001), corresponding to a 2.56-fold higher mortality risk in the low-ratio cohort (Figure 4 and Table 3). Compared to the low-ratio group, patients in the high M-MDSCs/PMN-MDSCs ratio group exhibited significantly reduced levels of total lymphocytes (0.570 [0.433–1.063] vs 0.850 [0.433–1.063] ×10^9/L; P = 0.006), CD4+ T cells (236.065 [130.750–396.933] vs 301.000

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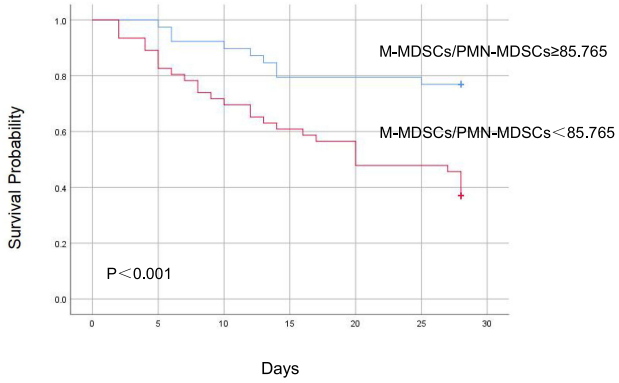

Figure 4 Kaplan-Meier 28-day survival curves based on high and low levels of M-MDSC/PMN-MDSCs.

[202.000–477.000] cells/μL; P = 0.048), CD8+ T cells (125.000 [66.818–190.953] vs 194.000 [144.000–341.440] cells/μL; P = 0.001), and NK cells (76.000 [41.908–157.500] vs 118.000 [73.000–222.000] cells/μL; P = 0.013), indicating systemic immunosuppression associated with elevated MDSCs ratios.

Stratification of critically ill patients based on combined M-MDSCs/PMN-MDSCs ratios (low: <85.765 vs high: ≥85.765) and APACHE II scores (low-risk: <24.5 vs high-risk: ≥24.5) identified four distinct prognostic subgroups: the high ratio + high APACHE II group (Group 1, 46.15% mortality), low ratio + low APACHE II group (Group 2, 41.67% mortality), low ratio + high APACHE II group (Group 3, 86.36% mortality), and high ratio + low APACHE II group (Group 4, 11.54% mortality). Notably, Group 3 demonstrated the highest 28-day mortality, exhibiting a 7.48-fold increased risk compared to Group 4 (86.36% vs 11.54%; hazard ratio [HR] = 7.48, 95% confidence interval [CI]: 4.82–11.62; P < 0.001), which robustly validates the synergistic prognostic value of integrating immune profiling (M-MDSCs/PMN-MDSCs ratios) with clinical severity scoring (APACHE II) for mortality risk stratification in critical illness (Figure 5).

Table 3 Comparison of Relevant Indicators Between High and Low M-MDSCs/PMN-MDSCs Level Groups

Characteristic	High Level Group	Low Level Group	χ2t/Z	p value
Number of patients	39	46	–	–
Gender, male	22	33	2.172	0.141
Age (years)	66.10±13.410	67.72±15.270	−0.513	0.609
Charlson comorbidity index (CCI)	4.000 (3.000,5.000)	4.000 (2.000,5.000)	−0.845	0.398
APACHE II score	24.000 (29.000,29.250)	21.000 (18.000,25.000)	−1.715	0.086
IL-6(pg/mL)	142.950 (80.570,349.975)	137.300 (45.300,380.000)	−0.317	0.751
Lac(mmol/L)	2.895 (2.000,5.020)	2.360 (1.450,3.450)	−1.543	0.123
CRP(mg/L)	151.380 (98.555,219.312)	108.690 (64.300,177.300)	−1.773	0.076
WBC(x10^9/L)	13.375 (9.393,18.562)	12.1100 (8.460,16.960)	−0.688	0.492
Neutrophils(x10^9/L)	11.895 (7.753,16.375)	10.2600 (7.080,15.440)	−0.767	0.443
lymphocyte(x10^9/L)	0.570 (0.433,1.063)	0.8500 (0.433,1.063)	−2.757	0.006*
$CD4^+$T cells(pcs/ul)	236.065 (130.750, 396.933)	301.000 (202.000,477.000)	−1.980	0.048*
$CD8^+$ T cells(pcs/ul)	125.000 (66.818,190.953)	194.000 (144.000,341.440)	−3.184	0.001*
B cells(pcs/ul)	141.910 (68.000,218.100)	144.000 (92.000,214.000)	−0.952	0.341
NK cells(pcs/ul)	76.000 (41.908,157.500)	118.000 (73.000,222.000)	−2.483	0.013*
Treg cells(%)	7.750 (6.175,10.050)	6.800 (5.300,9.800)	−1.319	0.187
Secondary infections	15 (38.46%)	17 (36.96%)	0.020	0.887
Length of ICU stay(days)	6.500 (4.000,13.250)	8.000 (4.000,12.000)	−0.009	0.993
Length of hospital stay(days)	16.000 (8.000,23.250)	16.0000 (12.000,25.000)	−1.337	0.181
Non-survivors	9 (23.08%)	29 (59.19%)	13.638	<0.001*

Notes: P<0.05 indicates statistical difference. *Indicating statistical differences.

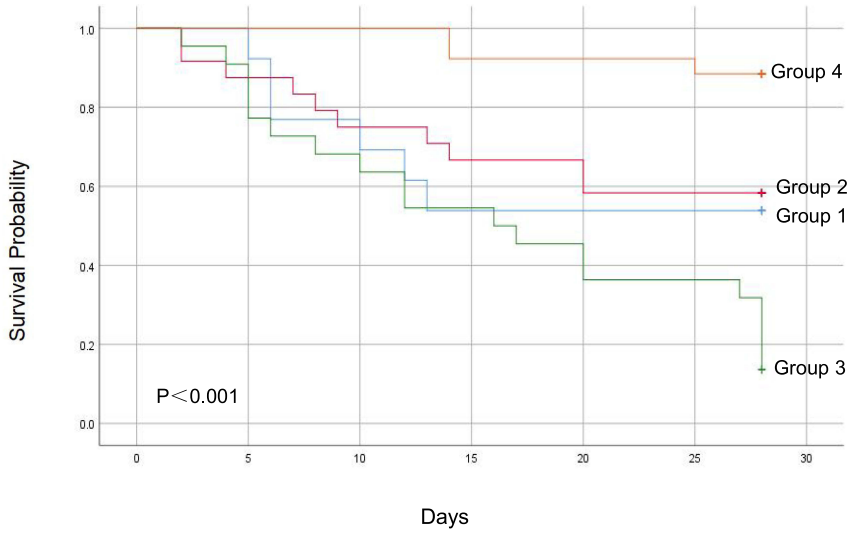

Figure 5 Kaplan-Meier 28-day survival curves based on combined stratification of M-MDSCs/PMN-MDSCs ratio and APACHE II scores:Group 1: High ratio + High APACHE II scores; Group 2: Low ratio + Low APACHE II scores; Group 3: Low ratio + High APACHE II scores; Group 4: High ratio + Low APACHE II scores.

Discussion

Myeloid cells originate from common myeloid progenitor cells derived from hematopoietic stem cells. Under normal physiological conditions, immature myeloid cells undergo rapid differentiation into dendritic cells, macrophages, and granulocytes, which migrate to target tissues to perform essential immune functions. In homeostasis, these immature myeloid cells lack immunosuppressive activity and predominantly reside in the bone marrow, with minimal presence in the peripheral circulation. Pathological conditions such as tumors, infections, trauma, or inflammatory disorders disrupt myeloid cell maturation, leading to the accumulation and systemic release of myeloid-derived suppressor cells (MDSCs). MDSCs have been extensively characterized in cancer biology, where their elevated levels in peripheral blood and tumor microenvironments correlate with advanced clinical stages, reduced survival rates, and metastatic progression across multiple malignancies, including renal, breast, hepatic, pancreatic, non-small cell lung cancers, and lymphomas.[12] Notably, circulating MDSC levels exhibit an inverse relationship with T-cell populations and serve as independent prognostic markers for solid tumors, irrespective of cancer type, subtype, or stage.[13] Higher peripheral MDSC proportions consistently predict poorer tumor outcomes,[13] and these cells have emerged as predictive biomarkers for both tumor progression[14,15] and therapeutic responsiveness.[16]

While MDSC biology in cancer is well-documented, their roles in critical illnesses—including sepsis, trauma, burns, and persistent inflammation-immunosuppression-catabolism syndrome (PICS)—remain poorly understood. To address this knowledge gap, our study focused on adult critically ill patients admitted to the ICU with APACHE II scores ≥15. We excluded confounding populations (pregnancy, active malignancies, transplant recipients, HIV infection, and individuals receiving immunosuppressive therapies) to isolate MDSC dynamics specific to early critical illness. This design enables systematic exploration of MDSC subgroup alterations during the acute phase of severe disease.

The activation of myeloid-derived suppressor cells (MDSCs) follows a sophisticated dual-signal paradigm. The canonical pathway is triggered by potent stimuli such as pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), manifesting transient activation characterized by intense phagocytic activity, respiratory burst, and release of pro-inflammatory cytokines (eg, IL-6, TNF-α), thereby mediating inflammatory responses. Upon recruitment to inflammatory sites, MDSCs initially suppress acute inflammation to promote resolution. However, persistent pathogen presence induces chronic MDSC activation, leading to systemic immunosuppression that significantly elevates susceptibility to infections and tumorigenesis.[17] Notably, MDSCs exhibit temporally dependent maturation of immunosuppressive capabilities: early-stage MDSCs (eg, during initial sepsis) predominantly display pro-inflammatory phenotypes with elevated nitric oxide (NO) and cytokines (IL-6, TNF-α), while late-stage MDSCs transition toward immunosuppression through increased secretion of anti-inflammatory mediators (Arg-1, IL-10) coupled with cellular immaturity.[18] A parallel phenomenon is observed in trauma patients, where sustained tissue damage and concomitant pro-inflammatory signaling

synergistically drive pathological MDSC activation, perpetuating an immunosuppressive or paralyzed immune state that markedly increases risks of sepsis progression, multi-organ failure, and mortality.[19,20] Mechanistically, MDSCs exert bidirectional immunomodulation through multimodal pathways: 1) Secretion of reactive oxygen species (ROS), matrix metalloproteinases (MMPs), arginase-1 (Arg-1), and cytokines (IL-6, IL-1β, VEGF); 2) Downregulation of NKG2D expression on NK cells via membrane-bound TGF-β,[21] coupled with Treg amplification to enhance immune tolerance;[22] 3) Competitive depletion of microenvironmental cysteine and L-arginine (via iNOS/Arg-1 pathways) to inhibit T-cell generation,[23] alongside ROS-dependent suppression of T-lymphocyte responses;[24] 4) Release of soluble factors (IL-10, TGF-β) that impair T/NK cell proliferation, cytotoxicity, and interferon production.[25]

While the majority of clinical studies emphasize the detrimental role of MDSCs in disease progression,[26,27] emerging evidence highlights their context-dependent protective potential in critical conditions. In critically ill patients, emergency myelopoiesis-driven expansion of MDSCs exerts protective effects by suppressing early-stage hyperinflammation,[28,29] as these cells combat infections through pathogen phagocytosis, reactive oxygen species (ROS) production, and bactericidal molecule secretion while simultaneously inhibiting systemic or local inflammation triggered by pathogenic or endogenous danger signals,[30–32] thereby achieving dual protection through accelerated pathogen clearance and tissue preservation. Experimental models further delineate tissue-specific reparative mechanisms: MDSCs suppress neuroinflammation via cerebral infiltration in traumatic brain injury;[33] M-MDSCs upregulate inducible nitric oxide synthase (iNOS) to produce nitric oxide (NO) in spinal cord injury, facilitating tissue repair through stem cell recruitment, collagen synthesis, and angiogenesis;[34–36] MDSCs mitigate pulmonary damage in thoracic trauma by inhibiting cell-mediated inflammation and antigen-specific T-cell responses;[37] early MDSC activation alleviates acute liver injury via downregulation of TNF-α/IFN-γ and upregulation of IL-10;[38] and MDSCs promote fracture healing by suppressing inflammatory T-cell proliferation while enhancing osteogenic transformation in orthopedic injuries.[39]

Our clinical observations provide critical validation: In ICU patients with APACHE II scores ≥15, survivors exhibited significantly higher early-stage monocytic MDSC proportions (M-MDSCs%) and M-MDSCs/PMN-MDSCs ratios compared to non-survivors, despite comparable baseline lymphocyte subsets (CD4+, CD8+, NK cells, Tregs). Notably, the M-MDSCs/PMN-MDSCs ratio demonstrated superior predictive efficacy for 28-day mortality over M-MDSCs% alone, with discriminative performance comparable to APACHE II scores. Stratified analysis using a predefined cutoff (≥85.765) revealed that the high-ratio group displayed significantly reduced lymphocyte counts (CD4+, CD8+, NK cells) yet achieved a 46% mortality reduction compared to the low-ratio group. These findings suggest that M-MDSCs-dominated immunosuppressive responses may confer protection during the early phase of critical illness by modulating T/NK cell functionality, thereby preventing excessive immune activation and subsequent tissue damage.

Emerging evidence demonstrates that myeloid-derived suppressor cells (MDSCs) exhibit a self-amplifying mechanism through cytokine network interactions: MDSCs produce IL-6, which not only promotes their own recruitment in vivo but synergizes with GM-CSF (granulocyte-macrophage colony-stimulating factor) and IL-13 to drive MDSC differentiation and expansion.[40] In vitro models confirm this regulatory loop—murine bone marrow cells cultured with G-CSF/GM-CSF proliferate and differentiate into M-MDSCs upon IL-6 or IL-13 stimulation,[41] while human peripheral blood mononuclear cells (PBMCs) similarly acquire MDSC phenotypes when exposed to GM-CSF and IL-6.[42] Functionally, PMN-MDSCs mediate antigen-specific immunosuppression,[43,44] whereas M-MDSCs suppress T-cell responses through both antigen-specific and nonspecific mechanisms involving nitric oxide (NO) and cytokine signaling.[45] Our clinical observations align with these mechanistic insights: Non-survivors presented with elevated IL-6, lactate, CRP, and M-MDSC levels alongside greater disease severity, suggesting MDSCs amplify pro-inflammatory cascades via non-specific T-cell inhibition, thereby reinforcing their own differentiation. Survivors exhibited favorable prognostic markers, including younger age, lower Charlson comorbidity indices, reduced APACHE II scores, and diminished inflammatory markers. Mortality risk correlated strongly with advanced age, polymorbidity, and elevated IL-6/CRP. Non-survivors showed higher secondary infection rates, likely attributable to increased invasive interventions, gastrointestinal dysfunction, and bacterial translocation risks. While ICU stays were comparable, survivors' prolonged hospitalization reflected extended convalescence from primary disease sequelae post-ICU discharge.

Critically ill patients often exhibit varying degrees of immune-inflammatory dysregulation, yet current clinical severity scoring systems (eg, APACHE II) lack immune-related biomarkers. This study innovatively integrated the

M-MDSCs/PMN-MDSCs ratio with APACHE II scores to establish a stratification model. Patients with M-MDSCs/PMN-MDSCs ≥85.765 and APACHE II <24.5 demonstrated the lowest mortality rate, whereas those with M-MDSCs/PMN-MDSCs <85.765 and APACHE II ≥24.5 exhibited the highest mortality. These findings confirm that this combined stratification strategy enhances prognostic accuracy and clinical assessment, providing an immunological dimension for clinical decision-making.

However, as a single-center exploratory study, several limitations must be acknowledged: 1) Restricted sample size; 2) Variability in blood collection timing (within 48 hours post-enrollment); 3) Potential confounding from pre-collection interventions affecting MDSC quantification stability. Additionally, MDSC heterogeneity and the absence of specific phenotypic/genomic markers[46,47] pose challenges in interpreting their clinical significance, while inconsistent phenotypic definitions across studies hinder comparative analyses. Nevertheless, this research highlights the potential value of MDSC monitoring in critical care immunomodulation and lays the foundation for future multicenter validation studies and the development of MDSC-specific molecular markers.

Conclusions

Elevated levels of M-MDSCs during the early phase of critical illness were observed to potentially exert protective effects. A higher ratio of M-MDSCs/PMN-MDSCs correlated with improved patient prognosis. This ratio demonstrated predictive value for 28-day mortality, positioning it as a potential biomarker for assessing disease severity and predicting outcomes in critically ill patients. However, as a single-center exploratory study with a limited sample size, these findings required validation through multicenter, large-scale cohorts to confirm MDSCs as a prognostic biomarker in such patients.

Data Sharing Statement

Data from this study is available from the corresponding Author by request.

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Disclosure

The authors report no conflicts of interest in this work.

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