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ORIGINAL RESEARCH

Sepsis with Cancer is Marked by a Dysregulated Myeloid Cell Compartment: A Pilot Study

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Background: Sepsis accounts for a significant proportion of global deaths and has limited treatment options. Cancer patients are at a higher risk of sepsis and experience worse outcomes, highlighting the complex interplay between sepsis and cancer on immune cell function and clinical prognosis.

Methods: Between July and December 2023, we prospectively enrolled 30 sepsis patients and 10 healthy controls, categorizing the patients into sepsis with non-cancer and sepsis with cancer based on established clinical diagnostics. Multi-color flow cytometry was used to monitor changes in the expression of surface molecules of monocyte and neutrophil subsets, phagocytic activity and cytokine-producing capacity.

Results: Compared with sepsis with non-cancer, the sepsis with cancer group demonstrated elevated 28-day mortality rates, increased $CD177^{+}$ activated band neutrophil and $HLA\text{-}DR^{low}CCR2^{low}$ classical monocyte, and attenuated phagocytic activity of immature neutrophil and monocyte. Further, $HLA\text{-}DR^{low}CCR2^{low}$ classical monocytes and $CD177^{+}$ myelocytes may serve as immunological predictors of adverse outcomes in sepsis. The $HLA\text{-}DR^{low}CCR2^{low}$ classical monocyte and $CD177^{+}$ myelocytes exhibit significant correlations with internal environment and coagulation markers.

Conclusion: In septic patients, particularly those patients with cancer, attenuated phagocytic activity of immature neutrophil (myelocytes, metamyelocytes, band neutrophils) and monocyte, and $HLA\text{-}DR^{low}CCR2^{low}$ classical monocyte and $CD177^{+}$ myelocytes may serve as immunological predictors of poor prognosis.

Keywords: sepsis, monocyte, neutrophil, cancer

Background

Sepsis, characterized by life-threatening organ dysfunction due to a dysregulated host response to infection,[1] is responsible for approximately 20% of global deaths prior to the COVID-19 pandemic.[2] Numerous randomized controlled trials have been conducted to improve the outcome,[3–6] however, current treatment options are limited to antibiotics and organ support therapy. The reasons are multifactorial, including diverse pathogens, genetic backgrounds, ages, sexes, environments, and comorbidities, indicating sepsis is a highly heterogeneous clinical syndrome with distinct phenotypes.[7–9] The individuals with cancer have a sepsis risk around tenfold higher than that of the general population.[10] It is well known that cancer and therapy for cancer (eg, chemotherapy, radiation, surgery, etc) increase the risk of sepsis.[11,12] Around 20% of sepsis hospitalizations were estimated to be linked with cancer.[13] In-hospital mortality was estimated to 1.5-fold higher (about 27.9%) in sepsis with cancer versus without cancer admissions.[13]

Previous studies have revealed that sepsis, with or without cancer, exhibits similar overall organ dysfunction, although there are differences in mortality. Patients of sepsis with cancer are more prone to hematological system dysfunction but are less likely to experience pulmonary or renal dysfunction.[14] The impact of cancer types on sepsis risk

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varies significantly. Patients with hematologic malignancies exhibit substantially higher sepsis incidence and mortality than solid tumor patients, primarily due to more severe immune impairment (particularly higher rates of neutropenia).[10] Although solid tumors generally confer lower risk, certain types (eg, lung cancer) are associated with higher sepsis-related mortality.[13]

Sepsis-induced immunosuppression is characterized by monocyte dysfunction, reduced dendritic cell (DC) numbers, and impaired DC activity.[6] Cancer patients inherently exhibit an immunosuppressive state, marked by lymphopenia and increased regulatory T cells and B cells, which sepsis further exacerbates.[15] In sepsis with non-cancer, early pro-inflammatory cytokine storms transition to anti-inflammatory cytokine, reflecting immune paralysis. In contrast, sepsis with cancer occurs against a backdrop of chronic low-grade inflammation, leading to higher baseline anti-inflammatory cytokine, increased G-CSF, and more profound immunosuppression, resulting in dysregulated inflammatory responses compared to sepsis alone.

Both sepsis and cancer have profound effects on myeloid cells, including neutrophils and monocytes, which are key components in defense against infection and/or cancer.[15,16] Neutrophils, the predominant leukocytes in peripheral blood, are the first recruited to infection sites, where they perform pathogen phagocytosis and clearance.[15] Monocytes exhibit plasticity, differentiating into macrophages or dendritic cells, and modulate inflammatory processes through cytokine and chemokine secretion.[16] At infection sites, these cells interact via cytokine networks, synergistically contributing to pathogen elimination, inflammation regulation, and tissue repair. In the previous studies, it was discovered that tumor-associated neutrophils exert dual functions: promote tumor progression through angiogenesis, extracellular matrix remodeling, metastasis and immunosuppression or exert anti-tumor efforts by direct killing of tumor cells.[17,18] Additionally, monocytes can engage with T cells and natural killer cells, impacting tumor progression by producing chemokines.[19–21] The reduction of HLA-DR expression was a key characteristic of monocytes in sepsis, and the responsiveness of monocytes to lipopolysaccharide (LPS) was severely diminished.[22,23] Under inflammatory conditions, immature cells of granulocytic and monocytic lineages can differentiate into myeloid-derived suppressor cells (MDSCs), the presence of which has been correlated with poor prognosis in multiple tumor types.[24–27] The presence of cancer complicates the clinical situation of sepsis and profoundly affects the immune response and outcomes in septic patients.

Considering the high in-hospital mortality rates and similar organ dysfunction in sepsis with cancer, whether immune dysfunction of the tumor-associated neutrophils and monocytes may contribute to clinical outcomes, which cannot be overlooked. In this pilot study, we attempted to investigate alteration of the subsets and immune functions of neutrophils and monocytes between sepsis with non-cancer (SNC) and with cancer (SC).

Materials and Methods

Study Design

In this study, thirty septic patients were recruited from the ICU of Beijing Ditan Hospital, Capital Medical University and Beijing Shijitan Hospital, Capital Medical University between July 2023 and December 2023. Ten age and sex matched healthy controls (HC) were recruited as controls at the Health Examination Center of Beijing Shijitan Hospital, Capital Medical University. Depending on whether they had solid cancer in diagnoses of ICU admission, septic patients were divided into the SNC (n = 19) and the SC (n = 11) (Figure 1). Patients were tracked until January 2024 to record the 28-day survival, infectious events, and the development of organ failure.

Inclusion and Exclusion Criteria

Diagnostic criteria for sepsis were:[1] 1) between the ages of 18 and 93; 2) Sequential Organ Failure Assessment (SOFA) score increased by 2 or equal to 2 when there is confirmed or suspected infection. Quick SOFA (qSOFA) uses 3 variables to predict patients at high risk of sepsis: a Glasgow Coma Score <15, a respiratory rate ≥22 breaths/min and a systolic blood pressure ≤100 mmHg; 3) The diagnostic criteria for septic shock were that vasopressor drug therapy is needed to maintain a mean arterial pressure >65 mmHg or a serum lactate level >2 mmol/L. This study was approved by the Committee of Ethics at Beijing Ditan Hospital and Beijing Shijitan Hospital, Capital Medical University. Blood samples and clinical data of patients were collected after obtaining informed consent of the patients and their families.

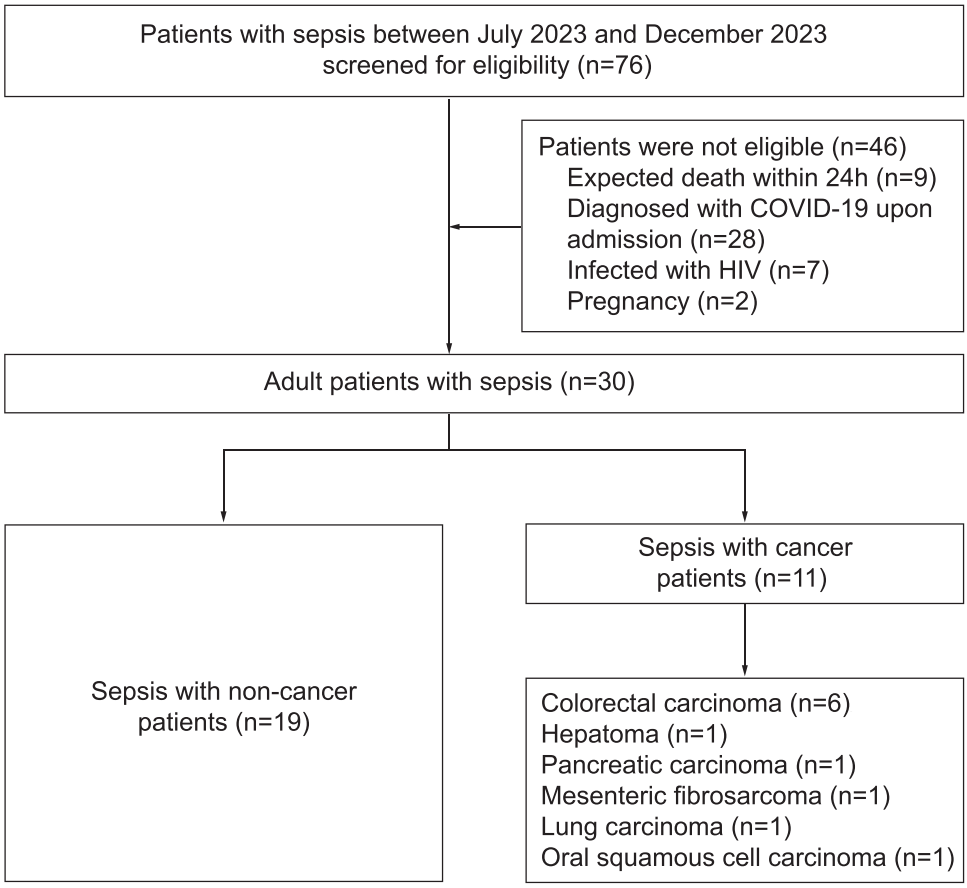

Figure 1 Flowchart of patients selection.

The following patients were excluded from this study: 1) patients with incomplete clinical data; 2) death within 24h; 3) diagnosed with COVID-19 upon admission; 4) patients with human immunodeficiency virus (HIV); 5) patients with successful resuscitation after sudden cardiac arrest; 6) pregnant women.

Neutrophil Isolation

We collected peripheral blood from HC and sepsis patients in tubes with EDTA. Using red blood cell (RBC) lysing solutions to isolate neutrophils and surface marker staining (CD16/CD10 with appropriate isotype controls).

Isolation of Peripheral Blood Mononuclear Cells (PBMCs)

We collected 8mL of peripheral blood from HC and sepsis patients in Vacutainer tubes with Ethylene Diamine Tetra acetic Acid (EDTA) and processed for PBMCs isolation. The blood was diluted 1:1 with phosphate buffered saline (PBS), layered onto Ficoll-Paque (GE Healthcare, Marlborough, MA, USA), and processed according to the manufacturer's instructions.

Flow Cytometric Analysis

Peripheral blood or freshly isolated PBMCs were incubated with directly conjugated fluorescent antibodies for 30 min at 4°C. Antibodies used included anti-human CD3-Percp-Cy5.5, CD15-Percp-Cy5.5, CD19-Percp-Cy5.5, CD45-FITC, CXCR4-FITC, CX3CR1-FITC, CD101-PE-Cy7, CCR2-PE-Cy7, CD10-PE, CD10-APC-Cy7, CD3-Alexa Fluor 700, CD45-Alexa Fluor 700, CD14-APC, CD177-APC, CD14-BV605, CD62L-BV605, CD16-BV510, HLA-DR-BV421, CD62L-BV421 (BioLegend, San Diego, CA, USA), TNF-α-FITC, IL-6-PE-Cy7 (eBioscience, San Diego, CA, USA), TIM3-APC-Cy7 (BD Bioscience, San Diego, CA, USA). The cells were washed before BD FACSCanto flow cytometry

(BD Bioscience, San Diego, CA, USA) analysis.[28,29] The gating strategy applied is shown in Figure S1. FlowJo software (Tree Star, Ashland, OR, USA) was used to analyze the flow cytometry data. GraphPad Prism 9 (GraphPad Software, USA) and R program were used to perform the graphing and statistical analysis.

Multicolor Flow Cytometry Dimensionality Reduction and Clustering Analysis

Using FlowJo 10.8.1 DownSample plugin, mononuclear cells were subsampled at 3000 cells/sample. The subsampled data were then merged into a single file using Conculation program. The merged file was subsequently analyzed using UMAP dimensionality reduction and FlowSOM clustering for data visualization. The FlowSOM clustering analysis strategy included data preprocessing, parameter optimization, clustering (using markers: CD14, CD16, HLA-DR, TIM3, CD62L, PD-L1, CCR2, and CX3CR1), as well as result evaluation and application.

Phagocytosis Assay

Latex Beads (Carboxylate-modified, Yellow-green, Sigma, USA) were added to peripheral blood and incubated in a carbon dioxide incubator at 37°C for 3 hours; placed on ice for 10 minutes to stop phagocytosis and then washed twice with PBS buffer. The corresponding cell surface fluorescent antibody combination was added and allowed to incubate at 4°C for 15 minutes in the dark. The ratio of beads (+) cells in neutrophils and monocytes were detected and analyzed using a flow cytometer to determine the phagocytic capacities.[29,30]

In vitro Stimulation and Intracellular Staining

For block the secretion of cytokines, Golgiplug (BD Bioscience, USA) was added to the PBMCs suspension. PBMCs were cultured in RPMI-1640 media (GIBGO, USA) containing 10% fetal bovine serum (FBS), with or without LPS (100 ng/mL, STEMCELL Technologies, Canada) for 3 hours. Cell stained with surface and intracellular antibodies, and the corresponding isotype controls. Data acquisition was performed on BD FACSCanto flow cytometry (BD Bioscience, USA), and data were analyzed with FlowJo software (Tree Star, USA).

Measures of Blinding

This study employed a double-blind design. During sample processing, researchers were unaware of participants' group assignments, with samples labeled by anonymous codes known only to an independent third party. Throughout data analysis, statisticians remained blinded to group allocation to minimize subjective bias.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR, 25th to 75th percentile). Statistical analyses were performed using GraphPad Prism 9 (GraphPad Software, USA) and the R program (https://cran.r-project.org/). For comparisons between two unpaired groups, the Wilcoxon test was utilized. Paired data were analyzed using the paired sample *t*-test. When comparing more than two groups, one-way ANOVA was applied. Data that were not normally distributed were presented as median and IQR. The Mann–Whitney *U*-test was used for comparisons between two unpaired groups, while the Wilcoxon signed-rank test was used for paired data. Descriptive statistics and Spearman's rank correlation coefficients were employed to assess correlations. A *P*-value of less than 0.05 was considered to indicate statistical significance. To control for multiple comparisons, *P*-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) correction method (Supplemental Table 1).

Results

Characteristics of Patients

To study the immune profile in sepsis with or without cancer, we enrolled thirty septic patients between July and December of 2023. Demographic information and characteristics of these patients were shown in Table 1 and septic patients have a median age of 72 years old (IQR: 66–81) years, with men accounting for 51.8%. Based on evidence of cancer in diagnoses of ICU admission, we classified septic patients into two groups: sepsis with non-cancer group (SNC)

Table 1 Basic Clinical Characteristics of Patients

		Total Patients (n=30)	Sepsis with Non-Cancer (n=19)	Sepsis with Cancer (n=11)	*P* value
Demographic	Age, y, median (IQR)	72 (66–81)	75 (67.8–84)	70 (62–81)	0.40
	Male n, (%)	14 (51.81)	8 (50)	6 (54.52)	1.00
Comorbidity	Hypertension n, (%)	16 (59.33)	11 (68.71)	5 (45.52)	0.26
	Diabetes n, (%)	15 (55.62)	10 (62.54)	5 (45.53)	0.45
	CHD n, (%)	10 (37.12)	7 (43.73)	3 (27.34)	0.45
	CRD n, (%)	3 (11.11)	1 (6.22)	2 (18.28)	0.55
	CLD n, (%)	7 (25.94)	6 (37.56)	1 (9.12)	0.18
	CKD n, (%)	4 (14.8)	4 (25)	0 (0)	0.12
	ND n, (%)	10 (37.13)	5 (31.36)	5 (45.53)	0.69
SOFA	Median (IQR)	4 (3–5)	4 (3–6)	3 (2–4)	0.07
Initial vital signs	BT (°C), mean (SD)	37.32 (0.91)	37.53 (0.81)	37.13 (0.95)	0.11
	HR (per minute), mean (SD)	102.63 (18.85)	97.42 (16.92)	110 (19.73)	0.06
	MAP (mmHg), mean (SD)	87.71 (19.24)	86.86 (20.84)	89.16 (17.47)	0.84
	RR (per minute), mean (SD)	24.98 (4.53)	24.42 (4.86)	25.65 (4.19)	0.24
	SpO_2 (%), mean (SD)	95.23 (3.44)	94.93 (4.16)	95.65 (2.36)	0.92
Internal environment	pH, mean (SD)	7.41 (0.12)	7.42 (0.13)	7.52 (0.12)	0.01
	pO_2 (mmHg), mean (SD)	126.32 (37.71)	128.83 (35.22)	122.61 (42.63)	0.86
	pCO_2 (mmHg), mean (SD)	32.81 (6.43)	32.22 (6.01)	33.72 (7.13)	0.69
	BE (mmol/L), median (IQR)	−1.85 (−8-2)	−3.42 (−8.50–0.16)	1.12 (−0.82–3.23)	0.02
	Lactate (mmol/L), median (IQR)	1.91 (1.34–3.13)	1.92 (1.31–3.01)	1.92 (0.92–3.64)	0.79
Blood routine index	WBC (10^9/L), mean (SD)	13.72 (7.12)	14.93 (7.92)	11.94 (5.54)	0.42
	NEU (10^9/L), mean (SD)	12.12 (6.83)	13.15 (7.77)	10.64 (5.32)	0.37
	NEUT (%), mean (SD)	86.32 (7.42)	86.12 (8.13)	86.76 (6.53)	0.71
	LYM (10^9/L), mean (SD)	0.93 (0.51)	1.02 (0.51)	0.82 (0.41)	0.47
	LYM (%), mean (SD)	8.21 (5.72)	8.41 (6.21)	7.84 (4.92)	1.00
	MNC (10^9/L), mean (SD)	0.71 (0.42)	0.71 (0.45)	0.63 (0.41)	0.31
	MNC (%), mean (SD)	5.15 (2.57)	4.92 (2.23)	5.25 (3.12)	0.78
	RBC (10^{12}/L), mean (SD)	3.45 (0.82)	3.44 (0.87)	3.31 (0.94)	0.90
	Hemoglobin (g/L), mean (SD)	101.32 (24.12)	100.96 (22.34)	101.81 (27.62)	0.79
	PLT (10^9/L), mean (SD)	185.43 (75.12)	159.65 (72.42)	222.91 (64.73)	0.02
Liver function index	TBIL (μmol/L), median (IQR)	18.81 (13.12–45.73)	21.63 (13.62–153.61)	16.52 (11.45–23.14)	0.49
	TP (g/L), mean (SD)	56.52 (7.34)	56.93 (7.12)	56.12 (7.91)	0.47
	ALT (U/L), median (IQR)	17 (11–63)	22 (11–122)	14 (8–34)	0.47
	AST (U/L), median (IQR)	26 (13–69)	31 (13–295)	17 (6–49)	0.26
Renal function index	Creatinine (μmol/L), mean (SD)	110.51 (89.32)	134.52 (109.36)	75.66 (23.82)	0.32
	K^+ (mmol/L), mean (SD)	3.92 (0.71)	4.15 (0.82)	3.83 (0.65)	0.19
	Na^+ (mmol/L), mean (SD)	136.96 (5.63)	136.42 (5.35)	137.71 (6.17)	0.55
	Cl^- (mmol/L), mean (SD)	103.12 (7.17)	103.92 (7.83)	101.96 (6.14)	0.43
	Ca^{2+} (mmol/L), mean (SD)	2.12 (0.14)	2.16 (0.14)	2.12 (0.17)	0.86
	Blood Glucose (mmol/L), mean (SD)	10.78 (3.82)	11.32 (3.71)	9.87 (4.14)	0.37
Coagulation function index	PT (s), mean (SD)	17.82 (8.81)	18.12 (8.14)	17.46 (10.12)	0.51
	PTA (%), mean (SD)	64.35 (23.32)	63.12 (25.76)	60 (20.67)	0.57
	APTT (s), mean (SD)	36.96 (13.44)	36.63 (12.21)	37.34 (15.48)	0.57
	Fib (g/L), mean (SD)	3.83 (1.85)	3.21 (1.43)	4.67 (2.21)	0.06
	INR, mean (SD)	1.62 (0.81)	1.78 (0.71)	1.61 (0.92)	0.63
	D-Dimmer (mg/L), mean (SD)	2.23 (2.36)	2.33 (2.75)	2.13 (1.62)	0.72
	TT (s), mean (SD)	16.12 (3.14)	16.51 (3.12)	15.67 (3.21)	0.27
Infection index	CRP (mg/L), median (IQR)	65.31 (34.62–189.71)	45.88 (23.11–128.27)	155.21 (65.45–247.91)	0.01
Infection site	Respiratory n, (%)	9 (33.33)	3 (18.72)	6 (54.64)	0.09
	Abdominal cavity n, (%)	14 (51.81)	10 (62.52)	5 (45.53)	0.45
	Other n, (%)	4 (14.84)	4 (21.05)	0 (0)	0.12
Type of cancer	Colorectal carcinoma	8 (26.67)	-	8 (72.73)	-
	Pulmonary carcinoma	2 (6.67)	-	2 (18.18)	-
	Oral cavity carcinoma	1 (3.33)	-	1 (9.09)	-

(*Continued*)

Table 1 (Continued).

		Total Patients (n=30)	Sepsis with Non-Cancer (n=19)	Sepsis with Cancer (n=11)	*P* value
Outcomes	28-day mortality n, (%)	9 (30)	3 (15.33)	6 (54.67)	0.03
	Hospital LOS (days), median (IQR)	9 (6–18)	8 (5–28)	10 (7–17)	0.67
	ICU LOS (days), median (IQR)	7 (4–12)	7 (4–12)	6 (4–20)	0.93

Abbreviations: CHD, coronary heart disease; CRD, chronic respiratory disease; CLD, chronic liver disease; CKD, chronic kidney disease; ND, neurological disease; SOFA, sequential organ failure assessment; BT, body temperature; HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; SpO_2, arterial oxygen saturation; pH, potential of hydrogen; pO2, oxygen partial pressure; pCO2, partial pressure of carbon dioxide; BE, base excess; WBC, white blood cell count; NEU, neutrophil count; NEUT, neutrophil percentage; LYM, lymphocyte count; LYM(%), percentage of lymphocytes; MNC, monocyte count; MNC(%), monocyte percentage; RBC, red blood cell count; PLT, platelet count; TBIL, total bilirubin; TP, total protein; ALT, alanine transaminase; AST, aspartate aminotransferase; K^+, serum kalium; Na^+, natriumion; Cl^-, chloridion; Ca^{2+}, calciumion; PT, prothrombin time; PTA, prothrombin activity; APTT, activated partial thromboplastin time; Fib, fibrinogen; INR, international normalized ratio; TT, thrombin time; CRP, C-reactive protein; ICU, intensive care unit; LOS, length of stay; IQR, interquartile range; SD, standard deviation.

(n = 19) and sepsis with cancer group (SC) (n = 11) (Figure 1). There was no significant difference in comorbidity, initial SOFA score and vital signs between two groups (Table 1). By comparing the internal environment of patients on the first day of diagnosis, it was observed that the potential of hydrogen (pH) in the SC group was significantly higher than that in the SNC group (7.45 ± 0.04 vs 7.38 ± 0.07, $P = 0.01$). And the base excess (BE) in the SC group was significantly higher than that in the SNC group (1.1 vs −3.4 mmol/L, $P = 0.02$). In addition, the platelet (PLT) count in the SC group was significantly higher than the SNC group (222.9 ± 64.7 vs 159.6 ± 72.410^9/L, $P = 0.02$). The level of the C-reactive protein (CRP) in the SC group was higher than that of the SNC group (155.2 vs 45.8 mg/L, $P = 0.01$). Despite no statistical differences were observed in liver, renal and coagulation function between SC and SNC group. In terms of mortality, the 28-day mortality for all septic patients was 30%, and the 28-day mortality of the SC group was significantly higher than that of the SNC group (54.6% vs 14.3%, $P = 0.03$). These results suggest that the SC group exhibit significant internal environment disorders, including elevated pH, BE, PLT, and CRP levels compared to the SNC group. Additionally, the higher 28-day mortality in the SC group highlights the poorer prognosis.

Expansion of Activated Band Neutrophil in SC Group

Compared to HC, septic patients exhibited increased proportion of neutrophils of nucleated cell ($P < 0.001$), neutrophil-to-lymphocyte ratio (NLR) ($P < 0.001$), and decreased proportion of lymphocyte of nucleated cell ($P < 0.001$) irrespective of whether SC or SNC (Figure S2A and S2B). First, to explore the effect of sepsis on the neutrophil subsets, we applied the multi-color flow cytometry to investigate the ability of phagocytosis among HC (n = 5), SNC (n = 11) and SC (n = 9). According to our previous study,[31] circulating neutrophils were divided into four subsets: myelocytes, metamyelocytes, band neutrophils, and segmented neutrophils based on the different expression levels of CD10 and CD16 (Figure S3A). Compared with the HC, SNC and SC displayed significantly decreased percentages of circulating mature neutrophils (segmented neutrophils; $P < 0.001$, $P < 0.001$), significantly increase in the proportions of immature neutrophils, including myelocytes ($P = 0.017$, $P = 0.021$), metamyelocytes ($P < 0.001$, $P = 0.005$), and band neutrophils ($P < 0.001$, $P < 0.001$) (Figure 2A). However, these differences were not observed between the SNC and SC. Additionally, we explored the phagocytic function of neutrophils subsets. We found that the phagocytic function of myelocytes were lower than other neutrophil subsets (Figures 2B, S3B and S3C). Compared to the SNC, the phagocytic function of band neutrophils in the SC was also impaired ($P = 0.031$) (Figure 2B).

Further, the expression of a mature marker CD101, activation marker CD177, CD62L, chemokine receptor CXCR2 in four neutrophil subsets were further analyzed. In HC group, segmented neutrophils exhibited expression of CXCR2, more that 95% segmented neutrophils were positive for CD101 and CD62L, and approximately 83% segmented neutrophils were positive for CD177 (Figures 2D, S4A–4C). The expression of CXCR2 of neutrophils subsets was comparable among HC, SNC and SC group (Figure S4D). Compared to HC, the proportion of CD101$^+$ band and segmented neutrophils were significantly decreased in SNC and SC group (band: $P = 0.033$, $P = 0.011$; segmented: $P = 0.038$, $P = 0.009$) (Figure 2D); the proportion of CD177$^+$ in myelocytes was significantly increased in SC and SNC group ($P = 0.032$, $P = 0.030$) (Figure 2C). Compared to SNC group, the proportion of CD177$^+$ in band neutrophils was significantly increased in SC

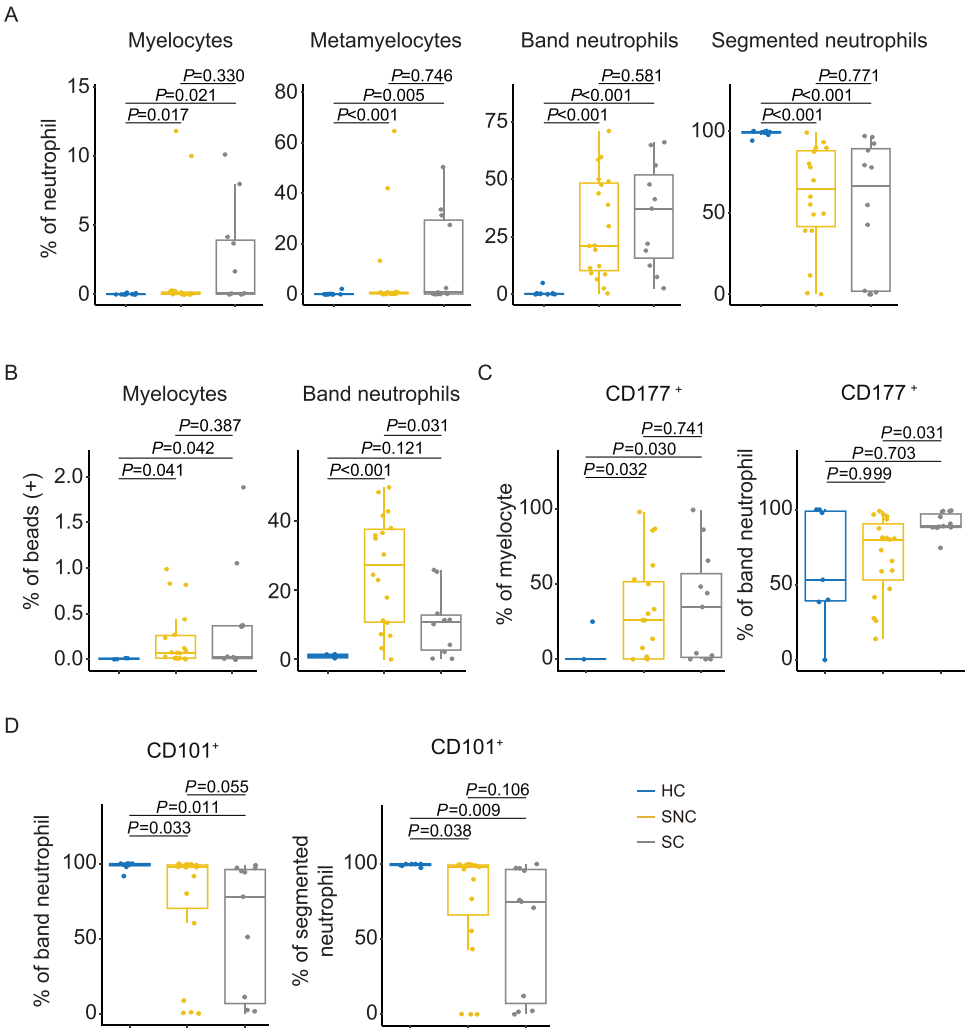

Figure 2 Characterization of the proportion, phagocytic capacity, activation and maturation of neutrophil subsets in healthy control (HC), sepsis with non-cancer (SNC) and sepsis with cancer (SC). (**A**) Comparison of the proportion of neutrophil subsets among healthy control (HC, n = 10), SNC (n = 19) and SC (n = 11). (**B**) Analysis of the myelocytes and band neutrophils phagocytic capacity by stimulating peripheral blood from HC (n = 4), SNC (n = 18), and SC (n = 10) with LPS (100 ng/mL) for 3 hours in *vitro*. (**C** and **D**) The proportions of $CD177^+$ in myelocytes and band neutrophils (**C**), and $CD101^+$ in band and segmented neutrophils (**D**) among HC (n = 7), SNC (n = 19) and SC (n = 11) were analyzed by flow cytometry. Statistical evaluation using Wilcoxon signed-rank test. *P*-values were adjusted using the Benjamini-Hochberg false discovery rate (FDR) correction method.

group ($P = 0.031$) (Figure 2C). Thus, sepsis induces release of immature neutrophils (myelocytes, metamyelocytes, band neutrophils) into the peripheral blood and band neutrophils in SC group display a more activated phenotype.

Monocytes in Septic Patients Exhibit Hypophagocytosis and Impaired Cytokine Secretion

In addition, compared to HC, patients with sepsis exhibited decreased proportion of lymphocyte-to-monocyte ratio (LMR) ($P < 0.001$, $P < 0.001$) (Figure S2B). We applied the flow cytometry to investigate the ability of phagocytosis, and cytokine-secreting among HC (n = 6), SNC (n = 12) and SC (n = 10). Compared to HC, the phagocytic capacity of monocytes in septic patients was significant reduced ($P = 0.041$, $P < 0.001$). Further, compared with SNC group, SC group exhibited a more significant decrease in monocyte phagocytosis ($P = 0.037$) (Figures 3A and S5A). We further explored the effect of sepsis on the intracellular TNF-α and IL-6 secretion capacity of monocytes (Figures 3B, S5B and S5C). Compared with HC, the TNF-α secretion capacity of monocytes from SNC group was significantly decreased ($P = 0.044$) (Figure 3B). Given the above results, monocytes exhibit impaired phagocytosis and pro-inflammatory cytokine secretion capacity in the SNC and SC group, with a more pronounced phagocytosis impairment observed in the SC group.

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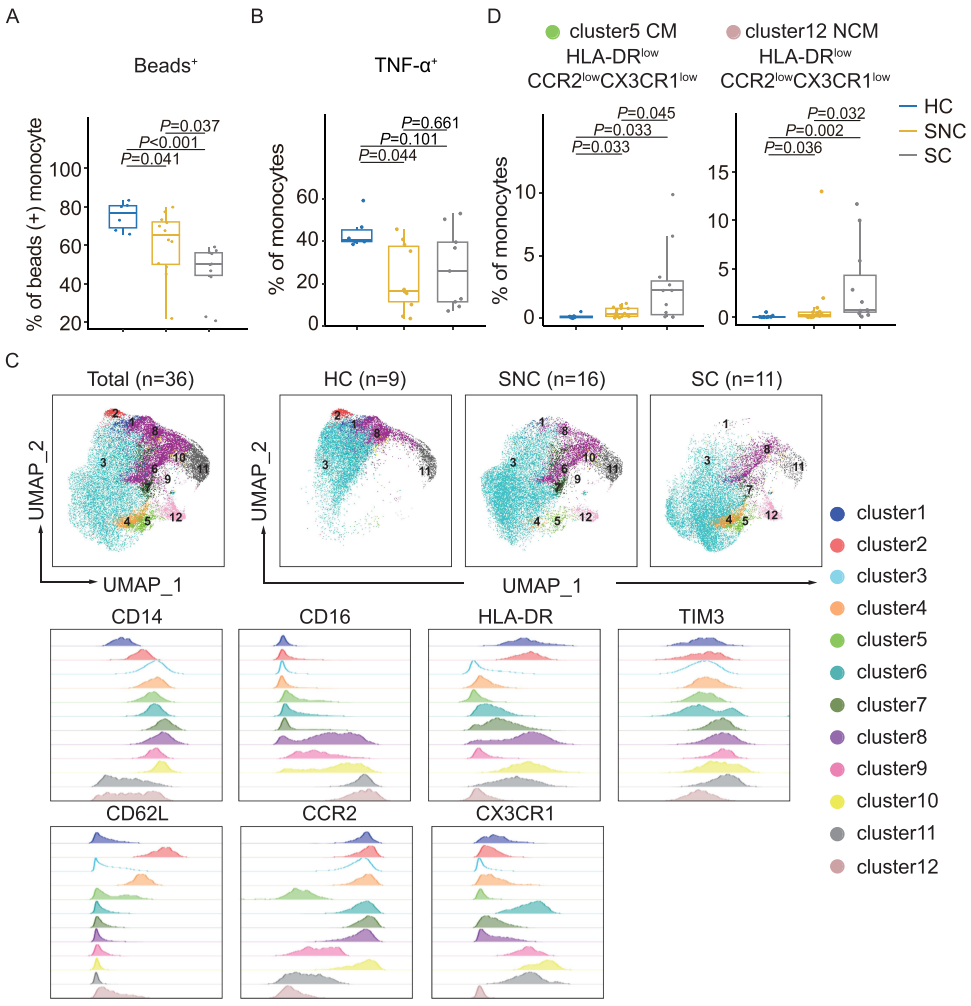

Figure 3 Characterization of the function of monocyte and the proportion of monocyte subsets in HC, SNC and SC. (**A**) Comparison of the monocyte phagocytic function by stimulating with LPS (100 ng/mL) for 3 hours in *vitro* from HC (n=6), SNC (n=12), and SC (n=10). (**B**) Intracellular staining for the percentage of TNF-α^+ monocytes by stimulating with LPS (100 ng/mL) for 3 hours in *vitro* from HC (n=6), SNC (n=10), and SC (n=9). (**C**) Flow cytometry data in a UMAP plot with FlowSOM clusters with cell identities established based on the expression displayed markers (CD14, CD16, HLA-DR, TIM3, CD62L, CX3CR1 and CCR2); 71070 live cells from HC (n=9), SNC (n=16), and SC (n=11) are shown after concatenation. (**D**) Boxplots of cluster 5 classical monocyte and cluster 12 non-classical monocyte subsets from HC, SNC, and SC. Statistical evaluation using Wilcoxon signed-rank test. *P*-values were adjusted using the Benjamini-Hochberg false discovery rate (FDR) correction method.

Emergence of HLA-DR^{low}CCR2^{low} Classical Monocyte in SC Group

To explore the effect of sepsis on the monocyte subsets, we used the UMAP and FlowSOM to analyze multi-color FCM data of monocyte from HC (n = 9), SNC (n = 16) and SC (n = 11) (Figure 3C). Unsupervised clustering analysis of all monocytes in all samples revealed 12 major clusters of CD14^{low}CD16^{-} immature monocytes (Mo0, cluster 1 and 2), CD14^{high}CD16^{-} classical monocytes (Mo1, cluster 3, 4, 5, 6 and 7), CD14^{high}CD16^{+} intermediate monocytes (Mo2, cluster 8, 9 and 10), and CD14^{low}CD16^{+} non-classical monocytes (Mo3, cluster 11 and 12) (Figures 3C and S6A). [32,33] The frequence of Mo0 (clusters 1 and 2) among monocytes was relatively low in HC, SNC and SC (Figure S6B). Compared with HC, the proportion of cluster 5 Mo1 (HLA-DR^{low}CCR2^{low}CX3CR1^{low}) (P = 0.033, P = 0.033) in SNC and SC was increased. Compared SNC, the percentage of cluster 5 Mo1 was significantly higher in SC (P = 0.045) (Figure 3D). The proportion of cluster 11 Mo3 (HLA-DR^{high}CCR2^{med}CX3CR1^{high}) in SC was significantly lower than that in HC (P = 0.017) (Figure S6B). The proportion of cluster 12 Mo3 (HLA-DR^{low}CCR2^{low}CX3CR1^{low}) in SNC and SC (P = 0.036, P = 0.002) was significantly higher than that in HC, and the change was more significant in SC (P = 0.032) (Figure 3D). No significant differences in other monocyte subsets were observed among the HC, SNC, and SC (Figure S6B). These results indicated that the emergence of HLA-DR^{low}CCR2^{low} classical monocyte in SC group with defective antigen presentation and chemotaxis.

The Elevation of HLA-DR^{low}CCR2^{low} Mo1 and CD177^{+} Myelocytes Might Indicative of Poor Outcomes

In our study, the 28-day mortality in sepsis with cancer was significantly higher than in sepsis with non-cancer (Figure 4A). To investigate the impact of myeloid cell subsets on the prognosis of the two patient groups, we conducted a subgroup analysis. In the forest plot of the subgroup analysis, we observed that no significant differences of survival outcomes were noted between SNC and SC (Figure S7A). To clarify whether myeloid cell subsets may predict patients' prognosis, the patients were divided into the survivor and the non-survivor group based on the 28-day mortality. We observed that the proportion and number of HLA-DR^{low}CCR2^{low} classical monocytes in the non-survivors were significantly higher than that in the survivor group (P = 0.032, P = 0.041), with an area under the receiver operating characteristic (ROC) curve of 0.722 and 0.782 (Figure 4B and 4C). Afterwards, the proportion and number of CD177^{+} myelocytes and in the non-survivors were significantly higher than that in the survivors (P = 0.034, P = 0.035), with an area under the ROC curve of 0.728 and 0.704 (Figure 4D and E). These results further highlighted that the elevation of percentage and numbers of HLA-DR^{low}CCR2^{low} Mo1 and CD177^{+} myelocytes maybe indicative of poor outcomes.

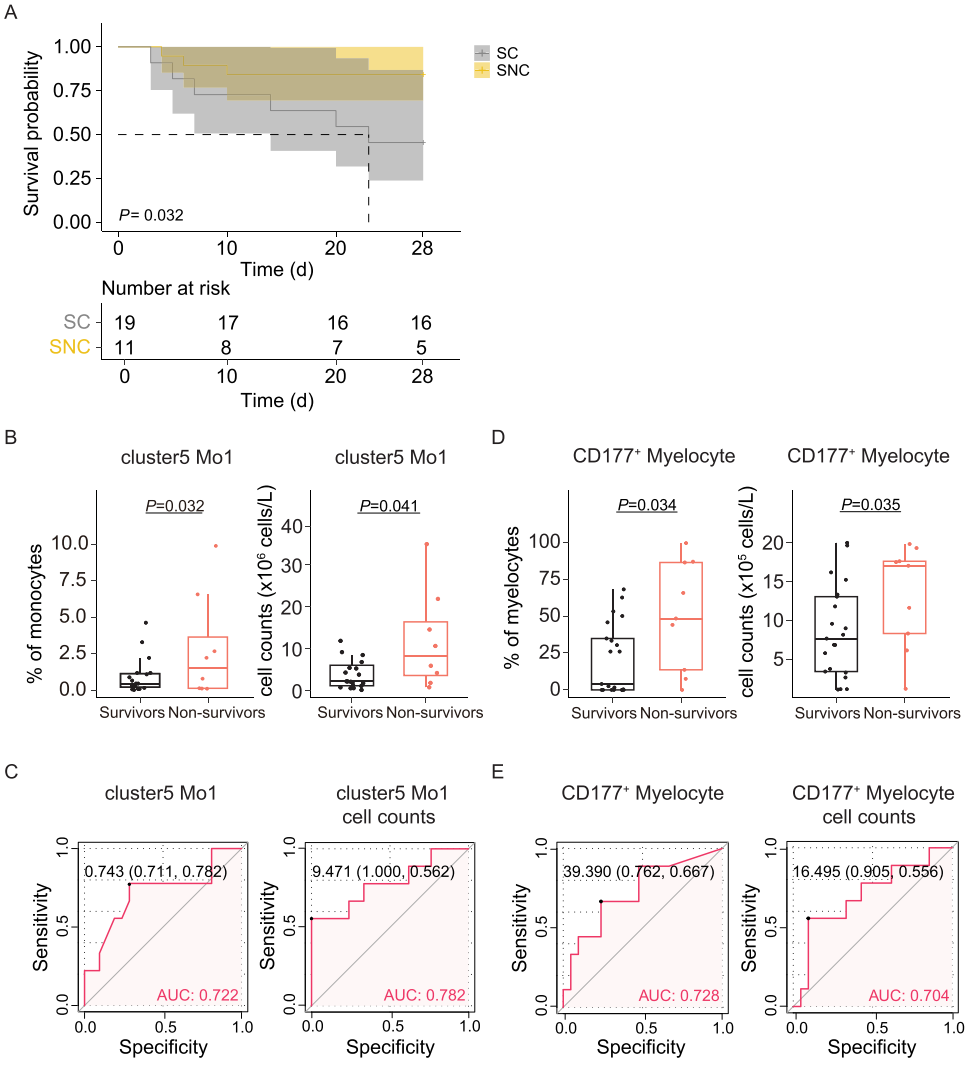

Figure 4 Cluster 5 classical monocytes and CD177^{+} myelocytes may indicative of poor outcomes. (**A**) Kaplan-Meier survival estimates at 28-days are provided for the SNC (n = 19) and SC (n = 11). (**B** and **D**) Boxplots of comparison between survivors (n = 21) and non-survivors (n = 9) in the proportion and cell counts of cluster 5 Mo1 (**B**) and CD177^{+} myelocytes (**D**). Statistical evaluation using Wilcoxon signed-rank test. (**C** and **E**) Predicted mortality at cluster 5 Mo1 (**C**) and CD177^{+} myelocytes (**E**). Curved red lines represent 95% confidence interval for predicted mortality at cluster 5 Mo1 and CD177^{+} myelocytes.

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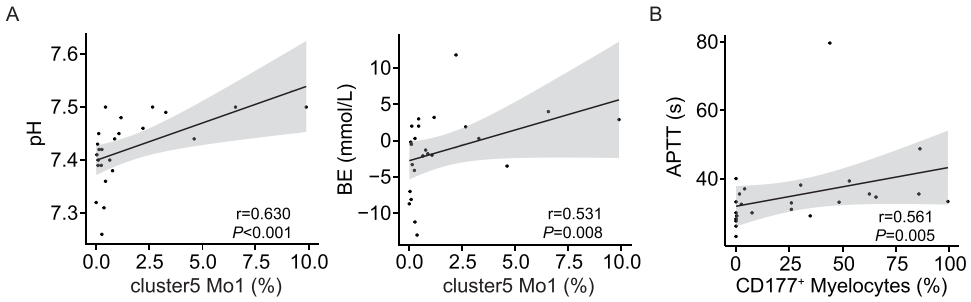

Figure 5 Correlation between cluster 5 classical monocytes and CD177$^+$ myelocytes with clinical laboratory indicators. (**A**) Positive correlation between cluster 5 Mo1 subsets with pH and BE. (**B**) Positive correlation between CD177$^+$ myelocyte with APTT. Spearman's rank correlation coefficients were employed to assess correlations.

Correlation between the Myeloid Subsets with Clinical Parameters

We further investigated the correlations between the percentage and numbers of myeloid subsets with thirty one critical clinical parameters, including blood gas test, blood routine test, biochemical test, as well as coagulation function test. Our findings indicated that higher proportion of HLA-DR^{low}CCR2^{low} classical monocytes was positively correlated with pH and BE ($P < 0.001$, $P = 0.008$) (Figure 5A). We observed that the proportion of CD177$^+$ myelocytes positively correlated with activated partial thromboplastin time (APTT) ($P = 0.005$) (Figure 5B). These results revealed that HLA-DR^{low} CCR2^{low} classical monocyte and CD177$^+$ myelocytes exhibit significant correlations with internal environment and coagulation markers.

Discussion

Patients suffering from both sepsis and cancer exhibit exacerbated physiological abnormalities and a markedly elevated 28-day mortality rate compared to septic patients without cancer. Our study provides a comprehensive analysis of the immunological landscape in septic patients, with a particular focus on those with concurrently diagnosed with cancer. In the sepsis cohort, significant alterations in the function and phenotype of CD177$^+$activated band neutrophil and HLA-DR^{low} CCR2^{low} classical monocyte were observed, which may indicate a dysregulation of the immune response. Furthermore, the HLA-DR^{low}CCR2^{low} classical monocyte and CD177$^+$ myelocytes correlated with internal environmental disorders and coagulation markers in sepsis patients, potentially serving as crucial biomarkers for diagnostic and prognostic evaluations.

In our study, we observed an overall mortality rate of 30% among the septic patient. The findings align with the previous studies, which have consistently demonstrated that the mortality rate among septic patients with cancer is markedly higher at severe infection and critical organ damage compared to those without cancer.[33,34] The mortality rate for SNC group was 15.3%, whereas for SC group, the rate was significantly higher at 54.6%. Our findings also reveal significant differences in blood pH levels and BE between the SNC and SC groups, which may indicate disturbances in metabolic and acid–base balance in SC patients. More studies have recognized that pH as a factor in cancer initiation and progression.[14,35,36] Cancer is an intriguing case in terms of the altered the intracellular pH (pH_i), as it has been well established that the pH_i of cancer tissue cells becomes basic (at 7.4 or 7.5).[37] The elevated pH/base excess in sepsis with cancer represents an underexplored metabolic phenomenon requiring mechanistic elucidation. Potential etiologies include: paraneoplastic metabolic alkalosis (such as ectopic hormone secretion and altered lactate metabolism); compensation for cancer-related chronic respiratory alkalosis; or chemotherapy-induced renal tubular dysfunction.[37] The characteristic hypochloremia of tumor-associated alkalosis contrasts with sepsis-related hyperchloremic acidosis, suggesting pathophysiological interplay. Furthermore, SC patients exhibited higher CRP levels, which could be associated with the inflammatory status of cancer patients. Consistent with previous studies, there is no significant difference in laboratory examination of organs function among septic patients, regardless of the presence of coexisting cancer.[38,39]

Our study confirmed the previous findings that sepsis is characterized by increased neutrophil proportion and NLR, along with reduced LMR, indicative of systemic inflammation and immune imbalance.[4,40,41] Both SC and SNC groups exhibited a decrease in mature neutrophils (segmented neutrophil) and increase in immature neutrophil subsets (myelocytes, metamyelocytes, band neutrophils), indicating a shift in the neutrophil developmental trajectory in response to the overwhelming

inflammation.[17,42] The decreased expression of CD101 on band and segmented neutrophils in SC and SNC groups suggests impairment of neutrophil maturation.[43,44] Meanwhile, our study has also observed the impaired phagocytic function of myelocytes and band neutrophils, especially in the SC group. The increased proportion of $CD177^+$ cells in myelocytes and band neutrophils in the SC group indicates an activated state, which may be a response to the underlying cancer or the sepsis itself.[43,45] More importantly, we found that the elevation of $CD177^+$ myelocytes might be indicative of poor prognosis. Previous studies have found that the proportion of $CD123^+$ immature neutrophils correlated with clinical severity in sepsis.[46] Although the activated myelocytes increased, their phagocytic function was significantly impaired. Therefore, the accumulation of the proportion and numbers of activated myelocytes did not enhance the pathogen clearance capability and further lead to a worse prognosis. This finding points to a potential mechanism by which sepsis with cancer impairs the innate immune response, leaving patients more susceptible to infections and contributing to the high mortality rates.[4,10] Previous studies have indicated that in sepsis, the counts of neutrophils may be associated with alterations in coagulation function. APTT, serving as a marker of coagulation function, may exhibit relation to the activity of neutrophils.[47] Furthermore, APTT is not merely an indicator of coagulation status but could also be a significant factor in evaluating the prognosis of sepsis patients.[48] Consistent with previous research, we also found that the negative correlation between $CD177^+$ myelocytes and APTT suggested a link between neutrophil dysfunction and coagulation in sepsis.

Our study found that the significant reduction in monocyte phagocytosis and cytokine secretion capacity in septic patients, especially in SC patients, which was consistent with previous studies. The classical monocytes express the chemokine receptor CCR2, while non-classical monocytes express the chemokine receptor CX3CR1.[30,49,50] The emergence of HLA-$DR^{low}CCR2^{low}$ Mo1 in SC group is a novel finding that warrants attention. The aberrant expression of CCR2 and CX3CR1 on classical monocyte might disrupt the migratory capacity of monocytes, thereby affecting their respond to infection in the tissue.[49,51] The positive correlation between HLA-$DR^{low}CCR2^{low}$ Mo1 and pH, as well as BE, suggests a link between monocyte dysfunction and internal environment disorder in sepsis with cancer. Additional studies have found that HLA-DR^{low} classical monocytes as biomarkers to predicted poor outcomes of sepsis.[22,52,53] Similar to the previous studies, our results further revealed that the percentage and numbers of HLA-$DR^{low}CCR2^{low}$ Mo1 as a predictor for 28-day mortality. Due to the limited cell numbers, HLA-$DR^{low}CCR2^{low}$ Mo1 were not explored by cell sorting and RNA sequence. We will further investigate the functions of HLA-$DR^{low}CCR2^{low}$ Mo1 with single-cell sequencing in the future. The results underscore the complexity of monocyte dysfunction in the context of sepsis and cancer, potentially involving multiple mechanisms that merit further investigation. The identification and investigation of these biomarkers could aid in the early recognition of high-risk patients, thereby guiding timelier and more targeted therapeutic interventions.

The integration of biomarkers in clinical management of sepsis patients with malignancies holds significant prognostic and therapeutic implications. Systematic monitoring of HLA-$DR^{low}CCR2^{low}$ classical monocytes and $CD177^+$ myeloid cells, combined with microenvironmental and coagulation markers (pH, BE, APTT), enables early risk stratification and dynamic assessment. These biomarkers reflect the severity of immune dysfunction, inflammatory status, and coagulopathy, facilitating timely therapeutic adjustments. Further optimization of anti-inflammatory and anticoagulant strategies can be achieved through biomarker-guided approaches. Future multicenter studies should validate these clinical utility of biomarkers and elucidate their molecular mechanisms to develop personalized therapies, ultimately improving survival and quality of life in this high-risk population.

However, this study has several limitations that warrant further refinement. First, the relatively limited sample size may significantly compromise statistical power, necessitating expanded cohort sizes in future studies to enhance result reliability. Second, substantial heterogeneity among cancer patients (including variations in pathological types, disease stages, treatment regimens, and immune status) could confound the interpretation of immune cell subset dynamics, underscoring the need for standardized stratified analyses in subsequent research. Currently, the findings remain predominantly descriptive, lacking mechanistic exploration of immune cell functional alterations; thus, integration of in vitro assays, animal models, and molecular techniques, such as single-cell sequencing and functional blockade experiments, is required for validation. Furthermore, the observational design precludes causal inference, highlighting the importance of future prospective cohort studies or immune cell-targeted interventional trials to evaluate the therapeutic potential of these cellular subsets.

Conclusions

In conclusion, our pilot study reveals the septic patients, particularly those patients with cancer, increased $CD177^{+}$ activated band neutrophil and HLA-$DR^{low}CCR2^{low}$ classical monocyte, decreased phagocytic activity of immature neutrophil and monocyte. And we found that HLA-$DR^{low}CCR2^{low}$ classical monocyte and $CD177^{+}$ myelocytes may serve as immunological predictors of poor prognosis. By identifying distinct monocyte and neutrophil subsets with potential prognostic significance, it advances our understanding of the immune profiles of sepsis with cancer. These findings are of great importance for improving outcomes in the high-risk populations.

Abbreviations

LPS, Lipopolysaccharide; MDSCs, Myeloid-derived suppressor cells; HC, Healthy control; SNC, Sepsis with non-cancer; SC, Sepsis with cancer; ICU, Intensive care unit; SOFA, Sequential Organ Failure Assessment; HIV, Human Immunodeficiency Virus; PBMCs, Peripheral Blood Mononuclear Cells; EDTA, Ethylene Diamine Tetra acetic Acid; PBS, Phosphate buffered saline; RBC, Red blood cell; FBS, Fetal bovine serum; UMAP, Uniform manifold approximation and projection; FlowSOM, Flow or mass cytometry analysis algorithm using a Self-Organizing Map; SD, Standard deviation; IQR, Interquartile range; FDR, False discovery rate; pH, Potential of Hydrogen; BE, Base excess; PLT, Platelet; CRP, C-reactive protein; NLR, Neutrophil-to-lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio; Mo0, immature monocytes; Mo1, classical monocytes; Mo2, intermediate monocytes; Mo3, non-classical monocytes; ROC, receiver operating characteristic; APTT, Activated Partial Thromboplastin Time.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethics committees or institutional review boards at Beijing Ditan Hospital, Capital Medical University and Beijing Shijitan Hospital, Capital Medical University approved the protocol and all amendments (NO.DTEC-KY2022-050-01 and I-22PJ091). All patients, or their legally authorized representatives, provided written informed consent. And our study complied with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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