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Relationship Between Sepsis Phenotypes and Treatment Characteristics of Patients with Viral and Bacterial Pneumonia

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Summary

New subgroups of patients with severe community-acquired pneumonia (SCAP) are hardly predicted by the use of clinical covariates; clusterization may significantly improve diagnostic approaches and facilitate the adaptation of specific treatment modalities to patient's individual characteristics.

The aim of the study. To identify linking the sepsis phenotype in patients with SCAP and preferable treatment option to forecasting the outcome and improve treatment results.

Materials and methods. Case histories of 664 intensive care unit (ICU) patients with sepsis (2016–2023) from I. I. Mechnikov Northwestern State Medical University were analyzed. The study included 568 (85.5%) patients with viral SCAP (SCAPv group) and 96 (14.5%) patients with bacterial SCAP (SCAPb group). Sepsis phenotypes were identified using algorithm proposed by Seymour C.W. et al. In SCAP cases associated with COVID-19 infection (*n*=293, 51.6%) patients received genetically engineered biological therapy (GEBT). The study compared two cohorts of patients: those who received GEBT and did not receive GEBT. Data were statistically processed using the Statistica 10.0 and SPSS software packages.

Results. Analysis revealed 4 sepsis phenotypes: α- (*N*=323, 48.6%); β- (*N*=128, 19.3%); γ- (*N*=87, 13.1%); δ- (*N*=126, 19%). The majority of SCAPv group patients — 295 (51.9%) — had α-phenotype of sepsis, while δ-phenotype prevailed in the SCAPb group — 53 (55.2%). The proportion of patients receiving GEBT and exhibiting α-sepsis phenotype dominated over other sepsis phenotypes: 61.8% of patientspossesed α-phenotype, whereas β-, γ- and δ-phenotypes were determined in 16% , 12.6%, and 9.6% of GEBT patients, respectivelty ($P<0.05$). The best effect of using monoclonal antibodies to interleukin-6 receptors as a GEBT was obtained in patients with the α-phenotype sepsis and COVID-19-associated SCAP: 87.5% favorable outcomes, $P=0.0419$. Rate of bacterial sepsis was significantly lower in patients with α- and δ-phenotypes of sepsis receiving GEBT vs those who did not receive this therapy: 12.71% vs 23.2% of patients with α-phenotype, $P=0.0131$; 25.0% vs 70.41% of patients with δ-phenotype, $P=0.0254$, respectively.

Conclusion. Differences in sepsis phenotype between patients with viral or bacterial SCAP may stratify patients for different therapeutic management and more accurately predict potential complications and unfavorable outcome.

Keywords: sepsis phenotypes; severe community-acquired pneumonia; genetically engineered biological therapy; response; outcome

Conflict of interest. The authors declare no conflict of interest.

Introduction

Community-acquired pneumonia (CAP) is one of the most common acute infectious diseases [1,2] accounting for a significant proportion of respiratory deaths [3]. The main causes of death in patients with severe community-acquired pneumonia (SCAP) are refractory hypoxemia, septic shock (SS) and organ dysfunction [4]. The host response to sepsis can be variable [5], which may partly explain the clinical heterogeneity that makes early diagnosis and treatment difficult [6]. Since the 2010s, numerous studies have been initiated worldwide to systematize sepsis and septic shock [7–11]. Current research is primarily focused on improving the accuracy of sepsis diagnosis using omics technologies [12], including the development of point-of-care testing systems [13]. Another critical aspect of clinical research is the collection of baseline phenotypes and patient trajectories using multivariate analysis techniques such as principal component analysis [14], factor analysis, and probabilistic [15] or consensus clustering [16]. Deep reinforcement learning has also emerged as an important area of study for assessing the continuum of organ dysfunction in sepsis [17]. The common trend among these initiatives is to assess patient trajectories, which includes investigating the prevalence of each phenotype and its impact on clinical outcomes such as long-term survival, resistance to vasopressor support, and duration of organ support [17–22]. The understanding of sepsis is complex and is aided by a variety of pattern recognition techniques used to identify sepsis subclasses. It should be noted that each newly derived subclass must be evaluated in the following

steps: 1) biological plausibility, 2) ability to predict treatment response, and 3) consistency and reproducibility across data sets [23]. The most reproducible study of sepsis phenotypes to date was that of Seymour et al. «Sepsis ENdotyping in Emergency CAre (SENECA)», which was conducted in multiple cohorts of patients from 12 centers over a 5-year period. The phenotypes were retrospectively replicated in cohorts with different types of sepsis and used in three randomized controlled trials (RCTs): ACCESS, PROWESS, and ProCESS. All three RCTs were multicenter and included extensive clinical data on sepsis biomarkers. The SENECA derivation cohort used matched k-means clustering models and showed that a 4-class model was most effective in distinguishing the α, β, γ, and δ phenotypes. The authors found that the identified sepsis phenotypes were associated with patient response to treatment as well as short-and long-term outcomes [24]. A study analyzed 42,735 patient data from the Multiparameter Intelligent Monitoring in Intensive Care-IV and eICU Collaborative Research Database to evaluate 79 Surviving Sepsis Campaign recommendations for four phenotypes (α, β, γ, and δ) in patients with sepsis and identify the most effective intensive care practices [25]. Bruse et al. studied 52,274 patients with sepsis and COVID-19 as well as three cohorts of patients with sepsis without COVID-19 (non-COVID-19 viral pneumonia sepsis, bacterial pneumonia sepsis, and bacterial sepsis of non-pulmonary origin) and found that dexamethasone was most effective in patients with the δ phenotype. Thus, the identification of phenotypes in SCAP will help to tailor therapeutic techniques [27] to the unique characteristics of patients [28].

The aim of our study was to identify sepsis phenotypes in patients with severe community-acquired pneumonia to improve treatment efficacy and prognosis.

Materials and Methods

During the study, we retrospectively reviewed 664 case histories of patients with SCAP admitted to the intensive care unit of I. I. Mechnikov Northwestern State Medical University between 2016 and 2023. There were 568 (85.54%) patients with viral SCAP and 96 (14.45%) with bacterial SCAP.

Sepsis and/or septic shock were confirmed according to the Sepsis-3 definition (https://jamanetwork.com/journals/jama/fullarticle/2492881). Retrospectively, SCAP phenotypes were differentiated using the algorithm proposed by Seymour et al. [24]. Patients were treated according to the provisional guidelines [29] and the guidelines of the Russian Federation of Anesthesiologists and Intensive Care Physicians [30].

The patients were assessed using Elixhauser Comorbidity Index (a measure of the overall severity of comorbidities that directly predicts length of hospital stay, hospital costs, and mortality), ATS/IDSA (American Thoracic Society/Infectious Diseases Society of America) minor criteria and the following scales: SOFA, APACHE IV (Acute Physiology And Chronic Health Evaluation IV), mNUTRIC (Modified Nutrition Risk in Critically Ill Score), NEWS2 (National Early Warning Score, British standardized assessment of patient severity based on 7 clinical parameters), A-DROP (Age, Dehydration, Respiratory failure, Orientation disturbance (confusion), and low blood Pressure, which is a modified version of the CURB-65 scale), SMART-COP (Systolic blood pressure, Multilobar infiltrate, Albumin, Respiratory rate, Tachycardia, Confusion, low Oxygen, low PH, which is an Australian model to identify patients requiring respiratory support and catecholamine infusion based on 8 clinical features), SAPS II (new Simplified Acute Physiology Score II, designed to assess severity and predict mortality in ICU patients), and GCS (Glasgow Coma Scale).

Data were analyzed using Statistica 10.0, SPSS, and Stat Research software packages at the Statistical Research Center in St. Petersburg, Russia. The Kolmogorov-Smirnov test was used to determine whether the distribution of variables was normal. Quantitative parameters with a normal distribution were expressed as arithmetic mean and standard deviation *($M\pm\sigma$)*. In the case of non-normal distribution, quantitative variables were reported as median *(Me)* and lower and upper quartiles *(Q1–Q3)*. The Mann–Whitney *U*-test was used to compare two independent groups. The Kruskal–Wallis test was used to test quantitative parameters for equality of medians across multiple samples. Qualitative parameters were compared between independent groups using Pearson's χ^2 and Fisher's exact test. The relationship between quantitative parameters was assessed using Spearman's rank correlation test. $P<0.05$ indicated significant differences between values.

Results and Discussion

Sepsis phenotypes were determined using 25 clinical and laboratory characteristics from 29 typical cluster variables in the SENECA data, as proposed by Seymour et al. (2019). The α-phenotype of sepsis had the lowest mortality rate and was the most common (48.6%) in the cohort, supporting the findings of Seymour et al. [24]. Fig. 1 shows the clustering of phenotypes based on 25 clinical and laboratory parameters.

The mean SOFA scores did not differ significantly between the viral and bacterial SCAP groups and was 5.34±2.73 points for all patients, whereas in the original study by Seymour et al. the SOFA score was lower at 3.9 points [24].

Among all patients, 4 sepsis phenotypes were identified: α (*N*=323, 48.6%); β (*N*=128, 19.3%); γ (*N*=87, 13.1%); δ (*N*=126, 19%). The α-phenotype

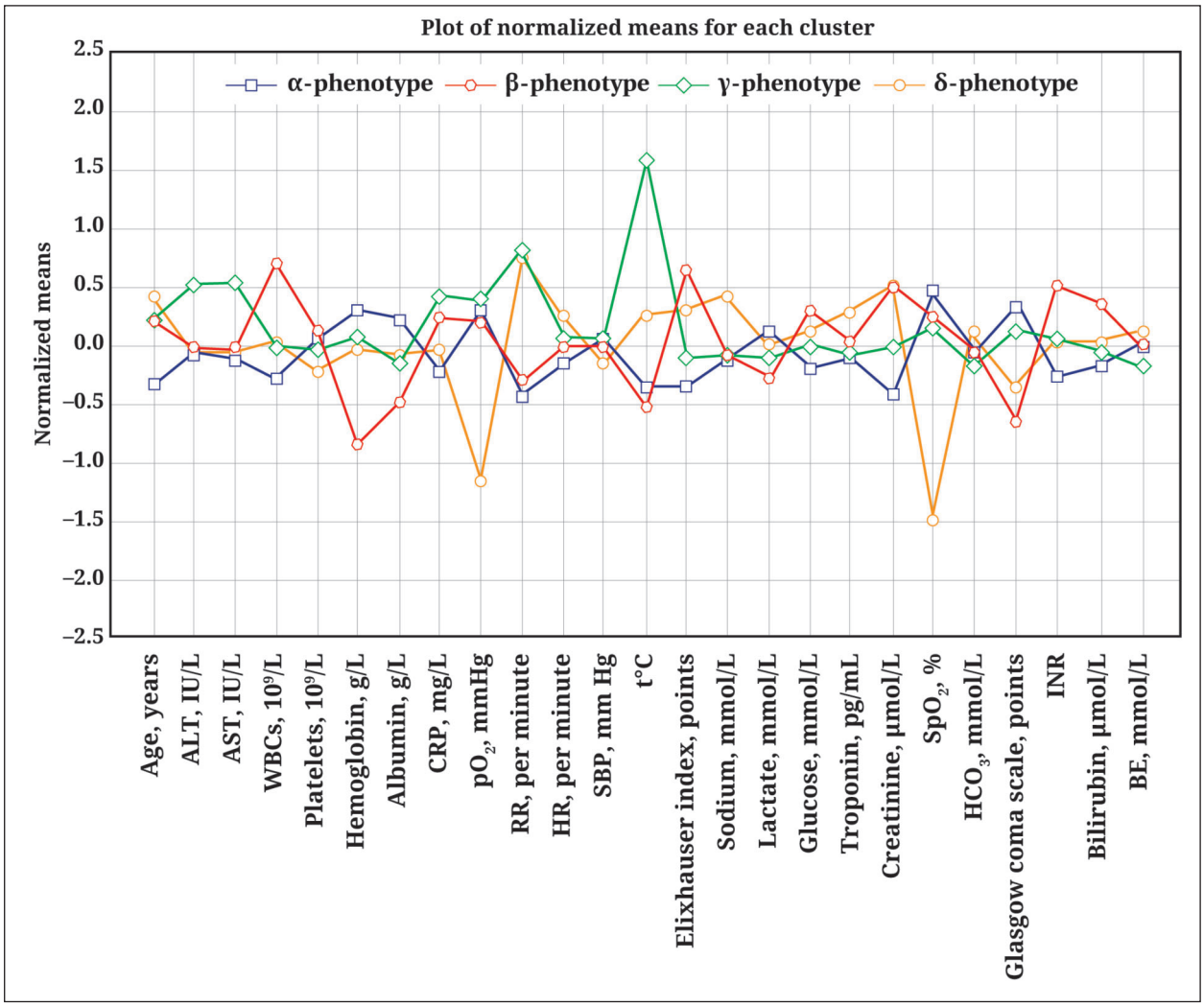

Fig. 1. Clusters of sepsis phenotypes based on 25 clinical and laboratory parameters.
Note. ALT — alanine aminotransferase; AST — aspartate aminotransferase; WBCs — white blood cells; CRP — C-reactive protein; pO_2 — partial pressure of oxygen; RR — respiratory rate; HR — heart rate; SBP — systolic blood pressure; t°C — temperature; SpO_2 — pulse oximetry; HCO_3 — bicarbonate; BE — base excess (or deficit); INR — international normalized ratio.

(*N*=295, 51.9%) was predominant in the vSCAP group, whereas the δ-phenotype (*N*=53, 55.2%) was most common in the bSCAP group.

The proportion of the β-phenotype of sepsis (19.3% of the entire patient cohort) was consistent with the study by Kalimouttou et al. [25], in which patients with the β-phenotype were highly prevalent and had the highest mortality rate (*N*=2022; OR 0.69; 95% CI: 0.50–0.94; *P*=0.01). In contrast, in a study by Bruse et al., in which the percentage of sepsis β-phenotype in the cohorts ranged from 1 to 4%, the α-phenotype was associated with the most favorable outcome, whereas the δ-phenotype was linked to the highest mortality [26].

As shown in Table 1, patients with sepsis α-phenotype were significantly younger in the vSCAP group than in the bSCAP group: 62.2±13.8 years vs. 71.3±13.4 years (*P*=0.001). Females with sepsis δ-phenotype were more frequent in bSCAP compared to vSCAP: 36 (67.9%) vs 34 (46.5%), *P*=0.0173.

Severe comorbidities with a mean Elixhauser Comorbidity Index score ⩾12 points were detected in the δ-phenotype in the vSCAP group and in the β-phenotype in the bSCAP group. Semicoma (SCH ⩽ 11 points) on admission was more common in sepsis β-phenotype in the bSCAP group. The highest score (⩾4 points) on the ATS/IDSA small criteria [31] was seen in sepsis β- and γ-phenotype in the bSCAP group.

Severe elevation of ferritin (1071 (518–1728) µg/L) was recorded in the β-phenotype of sepsis in the vSCAP group. The highest levels of procalcitonin (1.6 (0.5–2.5) ng/mL) and D-dimer (3.2 (2.0–4.4) µg/mL) were found in the γ-phenotype patients of the bSCAP group, and the highest levels of fibrinogen (6.2 (5.0–7.8) g/L) were observed in the γ-phenotype patients of the vSCAP group.

When comparing the APACHE IV scale scores [32] between the vSCAP and bSCAP groups, the highest score in the ß-phenotype of sepsis was recorded in the vSCAP group (126 (116-136) vs 112 (84.5–117.5), *P*=0.0484), and in δ-phenotype, in bSCAP group (123 (95–159) vs 87 (49–125), *P*=0.0014), in contrast to the study of Bruse et al. [26], where patients with β-phenotype sepsis had a mean APACHE IV score of 78 (62–98).

In the bSCAP group, the β-phenotype of sepsis was associated with longer ICU (19 (8.5–35.5) days) and hospital (19 (16.5–47) days) stays, and the longest duration of mechanical ventilation (23.5±27.0 days).

Most patients with β-phenotype sepsis required vasopressor support (6 [85.7%]) and reserve group antibiotics (7 [100.0%]). PaO_2/FiO_2 < 250 mmHg was documented in the majority of patients with α-, β-, γ-, and δ-phenotypes of sepsis in the vSCAP group, whereas only 62.5% of patients in the bSCAP group had similar values.

The lowest need for vasopressor support (norepinephrine at a dose above 0.5 μg/kg/min) was found in patients with the α-phenotype of sepsis in both vSCAP and bSCAP: 18 (6.1%) and 7 (25.0%) patients, respectively, *P*=0.0003. In patients with β-phenotype sepsis, high-dose vasopressor support was used more frequently in the bSCAP group than in the vSCAP group (85.7% vs. 43.8 %, *P*=0.0305).

Reserve group antibiotic use was ⩾85.5% in the α, β, and γ sepsis phenotypes in the bSCAP group. Significant differences in the frequency of reserve group antibiotic use were observed only between patients with α-phenotype sepsis in viral and bacterial SCAP (54 (18.3%) vs. 24 (85.7%) patients, *P*<0.0001). The ß-phenotype in the bSCAP group was associated with sepsis in all patients and invasive candidiasis in 4 (57.1%) patients.

The need for aggressive nutritional therapy with a high mNUTRIC score [33] was higher in patients with bSCAP than in those with vSCAP: α-phenotype 5 (4–6) vs. 3 (3–5) points, *P*=0.0002; β-phenotype 7 (7–8) vs 5 (4–6) points, *P*=0.0055; γ-phenotype 6.5 (4.8–8) vs 5 (3–6) points, *P*=0.0494; δ-phenotype 6 (5–7) vs 5 (4–6) points, *P*<0.0001. A high incidence (mean ⩾56.7%) of pulmonary embolism was observed with the β-phenotype in both SCAP groups. For all sepsis phenotypes, the duration of ICU stay was longer in the bSCAP group than in the vSCAP group (Table 1).

The highest number of poor outcomes was observed in β-phenotype of viral and bacterial sepsis, which was consistent with the study by Kalimouttou et al. [25]. In pairwise comparison, hospital mortality was higher in patients with α- and δ-phenotypes in the bSCAP group compared to those in the vSCAP group: with α-phenotype, 11 (39.2%) vs. 45 (15.2%), *P*=0.0013; with δ-phenotype, 33 (45.2%) vs. 34 (64.1%), *P*=0.0354.

Differences by sepsis phenotype between patients with viral and bacterial SCAP are shown in Table 1.

Clustering into 4 phenotypes of sepsis in COVID-19 SCAP patients in samples receiving (*N*=293) and not receiving (*N*=275) biologic therapy showed differences in severity of illness, length of hospital and ICU stay, complication rates, and mortality (Table 2).

The most commonly identified sepsis phenotype among COVID-19 SCAP patients receiving biologic therapy (BT) was the α-phenotype (*N*=181, 61.8%). They had a higher BMI of 30.6 (26.7–34.7) kg/m² compared to 26.9 (24.2–30.8) kg/m² (*P*<0.0001). A P/F index of 250 mmHg was found in 80.7% of the subjects who received BT and in 46.5% of those who did not receive BT (*P*<0.0001). We discovered that patients who underwent BT exhibited a significantly higher frequency of cancer and COPD compared to those who did not: 5 cases (2.8%) versus 11 cases (7.8%) for cancer (*P*=0.0405), and 5 cases (2.8%) versus 11 cases (7.8%) for COPD (*P*=0.0405), respectively. Patients who did not receive BT had higher D-dimer levels of 0.97 (0.4–2.3) μg/mL vs. 0.4 (0.2–1) μg/mL (P=0.0002), while fibrinogen levels were 6.4 (5.3–7.5) g/L vs. 5.5 (4.2–6.6) g/L (*P*=0.0005).

Patients who did not receive BT had a higher incidence of acute cardiovascular events and bacterial sepsis: 12 (9.7%) vs. 0 (0.0%) (*P*<0.0001) and 33 (23.2%) vs. 23 (12.7%) (*P*=0.0131).

Patients who received BT had a longer time from disease onset to ICU admission and a longer inpatient hospital stay: 10 (8–12) vs. 8 (6–14) days (*P*=0.0090) and 19 (15–27) vs. 18 (12–24) days (*P*=0.0203), respectively.

A NEWS2 [34] score > 8 on admission to the ICU was significantly higher in patients with α-phenotype sepsis who received BT: 172 (95.0%) vs 110 (78.0%) (*P*<0.0001), as well as the A-DROP scale *P*=0.0376) in contrast to the SMART-COP scale score [36] ⩾5 points, 11 (6.1%) vs. 21 (14.9%), (*P*=0.0087). The SAPS II scale score [37] was also statistically significantly higher in patients with α-phenotype sepsis who received BT, 28 (24–35) vs 26 (21–31.8) (*P*=0.0155).

Patients with β-phenotype sepsis represented only 16% (*N*=47) of the sample of patients receiving BT in COVID-19 SCAP and 26.9% (*N*=74) of the sample of patients not receiving BT.

Patients with β-phenotype sepsis who received BT were found to be hospitalized later than those who did not receive BT, at 12 (8–15) and 9 (4–14) days after onset, respectively.

Patients with β-phenotype sepsis were older than those with other sepsis phenotypes and their comorbidities were more severe. All patients with

Table 1. Comparison of sepsis phenotypes in viral and bacterial SCAP.

Parameter	Viral SCAP, *N*=568		Bacterial SCAP, *N*=96						*P*-value			
Phenotype	**α**	**β**	**γ**	**δ**	**α**	**β**	**γ**	**δ**	**P(α)**	**P(β)**	**P(γ)**	**P(δ)**
Total, *N* (%)	295 (51.9%)	121 (21.3%)	79 (13.9%)	73 (12.9%)	28 (29.2%)	7 (7.3%)	8 (8.3%)	53 (55.2%)				
Age, years *(M±σ)*	62.2±13.8	73.8±12.7	70.6±12.1	72.3±11.4	71.3±13.4	73.4±14.6	70.6±16.9	68.9±14.0	0.0010	0.8257	0.7023	0.2038
Sex, *N* (%)												
Women	135 (45.8)	63 (52.0)	33 (41.7)	34 (46.5)	13 (46.4)	6 (85.7)	2 (25.0)	36 (67.9)	0.9461	0.0825	0.3566	0.0173
Assessment scales, *Me (Q1–Q3)*												
SOFA (points)	4 (3–6)	6 (5–8)	6 (4–8)	6 (4–8)	2 (1–4)	2 (1–3.5)	5.5 (4.5– 6.3)	4 (3–7)	<0.0001	0.0004	0.7541	0.0030
EI (points)	4 (0–5)	8 (4–13)	5 (3–10)	12 (5–18)	4 (0–8)	13 (5–16.5)	8 (4–9)	10 (4–18)	0.8734	0.4876	0.4908	0.2854
GCS (points)	15 (15–15)	15 (13–15)	15 (14–15)	14 (13–15)	15 (15–15)	11 (8–15)	14.5 (13.8–15)	14 (8–15)	0.5674	0.1377	0.1641	0.1033
ATS/IDSA: minor criteria (points)	2 (2–2.5)	4 (3–5)	4 (2–4)	3 (2–4)	1 (0–2)	3 (3–4)	3.5 (2.8–4.5)	2 (1–3)	<0.0001	0.1099	0.7777	0.0173
mNUTRIC (points)	3 (3–5)	5 (4–6)	5 (3–6)	5 (4–6)	5 (4–6)	7 (7-8)	6.5 (4.8–8)	6 (5–7)	0.0002	0.0055	0.0494	<0.0001
APACHE IV (points)	52 (47–74)	126 (116–136)	95 (54.5–126)	87 (49–125)	70.5 (56.3–89.8)	112 (84.5–117.5)	110 (91.3–123.3)	123 (95–159)	0.0026	0.0484	0.6171	0.0014
SAPS II (points)	28 (22–34)	36 (31–43)	33 (30–39)	35 (28–40)	33.5 (27.8–38.5)	37 (36–43.5)	37.5 (31.8–37.5)	41 (33–53)	0.0093	0.4438	0.2860	0.0023
Laboratory parameters, *Me (Q1–Q3)*												
Ferritin, μg/L	716 (400–1345)	1071 (518–1728)	971 (455–1649)	987 (454–1767)	680 (680–680)			417.4 (129.3–606.0)	0.9437	1.0000	1.0000	0.0428
Procalcitonin, ng/mL	0.1 (0.1–0.3)	0.4 (0.2–1.2)	0.5 (0.2–3.7)	0.6 (0.2–1.7)	0.6 (0.2–2.3)	1.2 (0.2–3.1)	1.6 (0.5–2.5)	1.4 (0.6–5.3)	0.0001	0.3929	0.4314	0.0058
D-dimer, μg/L	0.5 (0.3–1.4)	1.5 (0.7–3.8)	1.8 (0.6–4.8)	1.8 (0.8–3.5)	1.4 (0.9–1.9)	1.2 (1.2– 1.2)	3.2 (2.0–4.4)	2.9 (0.7–6.4)	0.1751	0.7580	0.5651	0.4594
Fibrinogen, g/L	6.1 (4.7–7.4)	6.0 (4.6–7)	6.2 (5.0–7.8)	6.0 (4.2–7.7)	2.7 (2.1–4.0)	3.8 (3.1–3.8)	4.4 (4.3–5.1)	4.9 (3.1–7.2)	0.0005	0.0317	0.0979	0.2024
Intensive care												
Duration of RS, days, *M±σ*	4.1±4.0	7.7±5.9	5.8±3.9	4.7±4.5	2.8±3.0	23.5±26.9	5.8±4.9	4.8±10.1	0.1647	0.1152	0.9015	0.0150
P/F < 250 mmHg, *N* (%)	208 (70.5)	113 (93.3)	67 (84.8)	61 (83.5)	4 (14.2)	4 (57.1)	5 (62.5)	26 (49.0)	<0.0001	0.0009	0.1114	<0.0001
Vasopressor dose >0.5 μg/kg/min, *N* (%)	18 (6.1)	53 (43.8)	36 (45.5)	13 (17.8)	7 (25.0)	6 (85.7)	6 (75.0)	19 (35.8)	0.0003	0.0305	0.1124	0.0216
Reserve group antibiotics, *N* (%)	54 (18.3)	88 (72.7)	54 (68.3)	45 (61.6)	24 (85.7)	7 (100.0)	7 (87.5)	36 (67.9)	<0.0001	0.1088	0.2596	0.4676
Complications, *N* (%)												
PE	69 (23.5)	68 (56.6)	38 (48.1)	33 (45.2)	1 (3.7)	4 (57.1)	1 (12.5)	7 (13.2)	0.0170	0.9803	0.0537	0.0001
Bacterial sepsis	127 (43.0)	80 (66.1)	51 (64.5)	46 (63.0)	21 (75.0)	7 (100.0)	7 (87.5)	39 (73.5)	0.0012	0.0618	0.1896	0.2112
Invasive candidiasis	76 (25.7)	43 (35.5)	31 (39.2)	25 (34.2)	4 (14.8)	4 (57.1)	2 (28.5)	8 (15.0)	0.2076	0.2489	0.5780	0.0158
Length of stay and outcomes												
Re-transfer, *N* (%)	28 (9.5)	7 (5.8)	11 (13.9)	5 (6.8)	2 (7.1)	0 (0.0)	0 (0.0)	8 (15.1)	0.6824	0.5128	0.2588	0.1331
Days in ICU, *Me (Q1–Q3)*	4 (2–8)	7 (4–12)	7 (4–9.5)	5 (3–8)	10 (6.5–14.5)	19 (8.5–35.5)	8.5 (6.5–11)	6 (2–10)	<0.0001	0.0501	0.4258	0.4038
Days in the hospital, *Me (Q1–Q3)*	18 (14–25)	13 (8–21)	17 (9.5–25)	19 (9–27)	14.5 (10.5–18.3)	19 (16.5–47)	9 (5–10)	11.5 (4.8–20.5)	0.1363	0.1766	0.0586	0.0228
Unfavorable outcome, *N* (%)	45 (15.2)	115 (95.0)	43 (54.4)	33 (45.2)	11 (39.2)	7 (100.0)	6 (75.0)	34 (64.1)	0.0013	0.5462	0.2637	0.0354

Note. RS — respiratory support; PE — pulmonary embolism; EI — Elixhauser Index.

Table 2. Comparison of patients with different sepsis phenotypes in COVID-19 SCAP receiving (*N*=293) and not receiving (*N*=275) biologic therapy.

Parameter	COVID-19 SCAP receiving BT (*N*=293)				COVID-19 SCAP not receiving BT (*N*=275)				*P*-value			
Phenotype	**α**	**β**	**γ**	**δ**	**α**	**β**	**γ**	**δ**	***P*(α)**	***P*(β)**	***P*(γ)**	***P*(δ)**
Total, *N* (%)	181 (61.8)	47 (16.0)	37 (12.6)	28 (9.6)	114 (41.5)	74 (26.9)	42 (15.3)	45 (16.4)				
Patient characteristics												
BMI, kg/m², *Me (Q1–Q3)*	30.6 (26.6–34.6)	28.4 (25.3–31.1)	29.2 (26–33.2)	26.1 (24.1–32.7)	26.9 (24.2–30.8)	25.8 (23.0–29.8)	25.9 (23.5–31.8)	24.5 (23.4–28)	<0.0001	0.0183	0.0274	0.1448
Age, years, *M*±σ	63.8±15.0	74.9±12.7	71.2±12.9	72.9±12.5	61.1±12.8	72.1±12.5	69.9±11.3	71.2±9.6	0.0729	0.2111	0.4060	0.3850
Comorbidities, N (%)												
HTN and CHD	125 (69.0)	43 (91.5)	30 (81.0)	23 (82.1)	94 (66.2)	62 (76.5)	35 (70.0)	79 (80.6)	0.5846	0.0337	0.2398	0.8557
LC	6 (3.3)	4 (8.5)	0 (0.0)	0 (0.0)	4 (2.8)	5 (6.1)	2 (4.0)	13 (13.2)	0.7976	0.6180	0.2184	0.0418
Cancer	5 (2.7)	6 (12.7)	3 (8.1)	7 (25.0)	11 (7.7)	12 (14.8)	8 (16.0)	23 (23.4)	0.0405	0.7479	0.2735	0.8668
COPD	5 (2.7)	4 (8.5)	3 (8.1)	3 (10.7)	11 (7.7)	0 (0.0)	4 (8.0)	8 (8.1)	0.0405	0.0076	0.9854	0.6732
CRF	33 (18.2)	13 (27.6)	10 (27.0)	6 (21.4)	17 (11.9)	9 (11.1)	8 (16.0)	13 (13.2)	0.1226	0.0167	0.2094	0.2871
Assessment scales												
EI (points), *Me (Q1–Q3)*	4 (1–5)	5 (3.5–11)	5 (4–10)	12 (7.3–18.5)	4 (0–5)	10 (4–14)	6 (0–10.8)	12 (5–18)	0.4909	0.0126	0.9723	0.7759
GCS (points), *Me (Q1–Q3)*	15 (15–15)	15 (15–15)	15 (15–15)	15 (13–15)	15 (15–15)	13.5 (12–15)	15 (14–15)	14 (13–15)	0.0293	<0.0001	0.0102	0.7897
NEWS2 (points), *Me (Q1–Q3)*	9 (8–10)	10 (8–11.5)	9 (8–10)	9 (8–10)	8 (8–8)	9.5 (8–11)	9 (8–10)	8 (8–10)	<0.0001	0.8153	0.9755	0.2754
NEWS2 > 8 points, *N* (%)	172 (95.0)	47 (100.0)	36 (97.3)	27 (96.4)	110 (78.0)	69 (85.2)	43 (86.0)	59 (60.2)	<0.0001	0.0056	0.0714	0.0003
ATS/IDSA: minor criteria, (points), *Me (Q1–Q3)*	2 (2–3)	4 (3–4)	3 (2–4)	3 (2–3.3)	2 (1–2)	4 (3.3–5)	4 (2–5)	3 (2–4)	0.0088	0.0762	0.1219	0.8515
A-DROP ≥5 points, *N* (%)	17 (9.4)	9 (19.2)	2 (5.4)	6 (21.4)	5 (3.5)	16 (19.8)	5 (10.0)	9 (9.2)	0.0376	0.9338	0.4360	0.0776
SMART-COP ≥5 points, *N* (%)	11 (6.1)	13 (27.7)	6 (16.2)	8 (28.6)	21 (14.9)	38 (46.9)	15 (30.0)	49 (50.0)	0.0087	0.0320	0.1374	0.0445
SOFA (points), *Me (Q1–Q3)*	4 (3–6)	6 (4–8)	4 (3–6)	6 (4–8)	4 (4–6)	6 (5–9)	6 (5–8)	6 (4–8)	0.5191	0.0755	0.0002	0.8707
mNUTRIC (points), *Me (Q1–Q3)*	3 (3–5)	5 (4–6)	4 (3–5)	5 (3–6)	3 (3–5)	5.5 (4–6.8)	5 (4–6)	5 (4–6)	0.5420	0.1561	0.0010	0.2674
APACHE II (points), *Me (Q1–Q3)*	5 (5–14)	25 (25–26)	18 (5–25)	21 (5–25)	5 (5–14)	25.5 (25–28)	25 (6.75–26)	16 (5–25)	0.9268	0.4106	0.0781	0.4915
APACHE IV (points), *Me (Q1–Q3)*	54 (47–69)	125 (103–133)	88 (48–121)	91.5 (54.2–125)	49.5 (47–74)	127 (120–136)	113 (56.7–129)	76 (49–126)	0.7486	0.3115	0.0389	0.8692
SAPS II (points), *Me (Q1–Q3)*	28 (24–35)	33 (30.5–39)	32 (30–39)	35.5 (26–40.3)	26 (21–31.8)	38 (32–44.8)	34 (31–38.8)	34 (30–40)	0.0155	0.0021	0.5449	0.8736
Clinical and laboratory parameters												
SBP, mmHg (minimal), *Me (Q1–Q3)*	92 (69–100)	65 (51.5–100)	59 (56–100)	96.5 (83.7–100.2)	85 (69–97.7)	59 (45–84.7)	69 (48–93.7)	80 (56–96)	0.1210	0.0343	0.7374	0.0282
P/F < 250 mmHg, *N* (%)	146 (80.6)	47 (100.0)	31 (83.7)	25 (89.3)	66 (46.5)	70 (86.4)	41 (82.0)	62 (63.3)	<0.0001	0.0082	0.8276	0.0086
Lymphocytes (minimal), 10^9/L, *Me (Q1–Q3)*	0.8 (0.5–1)	0.6 (0.3–0.8)	0.7 (0.5–0.9)	0.65 (0.5–0.8)	0.9 (0.6–1.3)	0.6 (0.4–1.1)	0.6 (0.4–1)	0.6 (0.3–0.9)	0.0025	0.1006	0.4389	0.9864
Platelets below 100×10^9/L, *N* (%)	4 (2.2%)	5 (10.6%)	3 (8.1%)	1 (3.6%)	11 (7.8%)	14 (17.3%)	10 (20.0%)	14 (14.3%)	0.0189	0.3080	0.1240	0.1226
Ferritin, µg/L, *Me (Q1–Q3)*	905 (493–1550)	1247 (544–1923)	1171 (547–1888)	1150 (740–1863)	456 (323–975)	984 (456–1590)	711 (440–1202.5)	697.5 (341.25–1438.5)	<0.0001	0.4491	0.0655	0.0624
Procalcitonin, ng/mL, *Me (Q1–Q3)*	0.1 (0.1–0.2)	0.2 (0.1–0.4)	0.3 (0.1–0.6)	0.2 (0.1–0.7)	0.2 (0.1–0.5)	0.7 (0.4–2)	2.4 (0.3–7.2)	1.2 (0.4–4.1)	0.1061	<0.0001	0.0001	0.0005
Albumin, g/L, *Me (Q1–Q3)*	35 (32–38)	32 (29–35)	35 (32–37)	29 (26–32)	34 (30–38)	30 (25.7–32.3)	28 (25–31.8)	26 (22–30)	0.2244	0.0052	<0.0001	0.3495
CRP (maximal), mg/L, *Me (Q1–Q3)*	84 (41.5–147.6)	110 (66–167)	127.2 (63.9–185)	111.7 (75.5–167.6)	54.1 (18.6–128.9)	120 (73.2–169)	157 (119.9–204)	140.7 (81–175.9)	0.0023	0.6671	0.1568	0.4562
D-dimer, µg/mL, *Me (Q1–Q3)*	0.4 (0.2–1)	0.9 (0.5–3.0)	1 (0.4–3.9)	2.8 (1.0–5.0)	1.0 (0.4–2.3)	2.0 (1.1–4)	2.1 (0.9–5.2)	1.4 (0.8–2.9)	0.0002	0.0039	0.1016	0.0908
Fibrinogen, g/L, *Me (Q1–Q3)*	6.4 (5.3–7.5)	6.6 (5.4–7.5)	6.6 (5.8–8.2)	5.3 (4.0–6.9)	5.4 (3.9–7.2)	5.5 (4.2–6.6)	6.1 (4.6–7.1)	6.4 (4.4–8.1)	0.0005	0.0025	0.0661	0.1008
Troponin T, ng/mL, *Me (Q1–Q3)*	13 (8–28.5)	110.5 (34.8–580.2)	48 (23.1– 91)	73.5 (40–327.5)	19.8 (8.5–58)	104.7 (48.9–268.5)	39 (19–149)	71.2 (25–126.7)	0.1252	0.9837	0.9831	0.1859

Continuation Table 2.

Parameter	COVID-19 SCAP receiving BT (*n*=293)				COVID-19 SCAP not receiving BT (*n*=275)				*P*-value			
Phenotypes	**α**	**β**	**γ**	**δ**	**α**	**β**	**γ**	**δ**	***P*(α)**	***P*(β)**	***P*(γ)**	***P*(δ)**
Intensive care												
Duration of RS, days, *M±σ*	4.9±4.4	10.0±5.9	6.5±3.3	6.0±5.5	2.6±2.7	6.1±5.3	5.2±4.3	3.9±3.6	<0.0001	<0.0001	0.9262	0.1912
Dose of vasopressin >0.5 μg/kg/min, *N* (%)	16 (8.8)	23 (48.9)	19 (51.4)	5 (17.9)	4 (3.5)	35 (47.3)	17 (40.5)	10 (22.2)	0.9018	0.8545	0.6214	0.0074
Reserve group antibiotics, *N* (%)	27 (14.9)	33 (70.2)	22 (59.4)	13 (46.4)	51 (35.9)	62 (76.5)	39 (78.0)	68 (69.3)	<0.0001	0.4300	0.0618	0.0253
Complications, *N* (%)												
PE	44 (24.5)	27 (58.7)	13 (35.1)	17 (60.7)	26 (18.4)	45 (55.5)	26 (52.0)	23 (23.5)	0.1871	0.7314	0.1179	0.0002
CVE	0 (0.0)	1 (2.2)	3 (8.1)	0 (0.0)	12 (9.7)	7 (8.9)	4 (8.7)	11 (12.8)	<0.0001	0.1407	0.9237	0.0465
Bacterial sepsis	23 (12.7)	34 (72.3)	26 (70.3)	7 (25.0)	33 (23.2)	65 (80.2)	39 (78.0)	69 (70.4)	0.0131	0.3030	0.4122	<0.0001
Invasive candidiasis	50 (27.6)	24 (51.0)	14 (37.8)	10 (35.7)	30 (21.3)	23 (28.4)	19 (38.8)	23 (23.5)	0.1909	0.0103	0.9295	0.1937
Length of stay, frequency of re-transfers and outcomes												
Days from hospital to ICU admission, *Me (Q1–Q3)*	3 (1–6)	4 (1–6.5)	1 (1–3)	5.5 (1–12)	1 (1–2)	1 (1–4)	2 (1–7.75)	3 (1–10)	<0.0001	0.0513	0.0571	0.9023
Days from disease onset to ICU admission, *Me (Q1–Q3)*	10 (8–12)	12 (8–15)	9 (4–13)	10 (7.5–15.7)	8 (6–14)	9 (4–14)	8.5 (6–16)	9 (7–13)	0.0090	0.0576	0.2258	0.3109
Re-transfer, *N* (%)	15 (8.3)	6 (12.8)	7 (18.9)	2 (7.1)	15 (10.5)	1 (1.2)	4 (8.0)	11 (11.2)	0.4842	0.0057	0.1298	0.5312
Unfavorable outcome, *N* (%)	32 (17.7)	45 (95.7)	19 (51.3)	14 (50.0)	24 (16.9)	77 (95.0)	30 (60.0)	53 (54.0)	0.8545	0.8601	0.4213	0.7027
Days in ICU, *Me (Q1–Q3)*	5 (3–9)	10 (6–14)	9 (6–10)	6 (5–10)	3 (2–5)	6 (3–10)	5.5 (2.25–9)	4 (2–7)	<0.0001	0.0004	0.0289	0.0049
Days in hospital, *Me (Q1–Q3)*	19 (15–27)	17 (12.5–5.5)	16 (10–25)	20 (14.3–24.5)	18 (12–24)	11 (5.3–17)	17.5 (9–24.5)	17 (8–28)	0.0203	<0.0001	0.9529	0.2399

Note. HTN — hypertension; CHD — coronary heart disease; LC — liver cirrhosis; COPD — chronic obstructive pulmonary disease; CRF — chronic respiratory failure; PE — pulmonary embolism; CVE — cardiovascular events; CRP — C-reactive protein; NEWS2 — National Early Warning Score; ATS/IDSA — American Thoracic Society Criteria for Defining Severe Community-acquired Pneumonia; A-DROP — Age, Dehydration, Respiratory failure, Orientation disturbance (confusion), and low blood Pressure; SMART-COP — Systolic blood pressure, Multilobar infiltrate, Albumin, Respiratory Rate, Tachycardia, Confusion, low Oxygen, low PH; RS — respiratory support; SBP — systolic blood pressure; EI — Elixhauser Index; GCS — Glasgow Coma Scale.

β-phenotype sepsis had a P/F index less than 250 mmHg.

When comparing patients with β-phenotype sepsis who received BT to those who did not, the mean Elixhauser Index score was lower in those on BT at 5 (3.5–11) vs. 10 (4–14) (P=0.0126). Their Glasgow Coma Scale score was higher and corresponded to clear consciousness at 15 (15–15) vs 13.5 (12–15) points (P<0.0001). Patients who received BT had higher fibrinogen levels, 6.6 (5.4–7.5) g/L versus 5.5 (4.2–6.6) g/L (P=0.0025). Patients not receiving BT had higher levels of procalcitonin at 0.7 (0.4–2) ng/mL vs. 0.2 (0.1–0.4) ng/mL (P<0.0001) and D-dimer at 2.0 (1.1–4) μg/mL vs. 0.9 (0.5–3.0) μg/mL (P=0.0039). Patients with ß-phenotype receiving BT had a significantly longer duration of respiratory support (10.1±6.0 vs. 6.1±5.3 days, P<0.0001). Invasive candidiasis was diagnosed in 24 (51%) patients receiving BT versus 23 (28.4%) patients not receiving BT (P=0.0103). The rates of bacterial sepsis and pulmonary embolism were similar in both groups.

When we compared the severity of illness in patients with β-phenotype sepsis who received BT and those who did not, we found NEWS2 > 8 in 100.0% vs. 85.2% (P=0.0056) and SAPS II of 33 (30.5–39.0) vs. 38 (32.0–44.8) (P=0.0021), respectively. Patients with the β-phenotype of sepsis who received BT and those who did not had the same rate of adverse outcomes (95.7% vs. 95.0%, P>0.05), but a higher number of adverse outcomes than other sepsis phenotypes.

Patients with the γ sepsis phenotype in both samples had comparable age, Elixhauser Index, ATS/IDSA minor criteria, and SAPS II score. Patients with the γ phenotype who did not receive BT had higher mNUTRIC and APACHE IV scores of 5 (4–6) vs. 4 (3–5) (P=0.001) and 113 (56.7–129) vs. 88 (48–121) (P=0.0389), respectively. Patients who did not receive BT had significantly higher procalcitonin levels, 2.4 (0.3–7.2) ng/mL vs 0.2 (0.1–0.4) ng/mL (P<0.0001), and a shorter mean ICU stay, 5.5 (2.3–9) vs 9 (6–10) days (P=0.0289).

Patients with the δ-phenotype of sepsis in both samples were comparable in age, Glasgow Coma Scale, ATS/IDSA minor criteria, mNUTRIC scale, APACHE IV, and SAPS II. Elixhauser Index and D-dimer levels were higher than in other phenotypes. Pulmonary embolism was the most com-

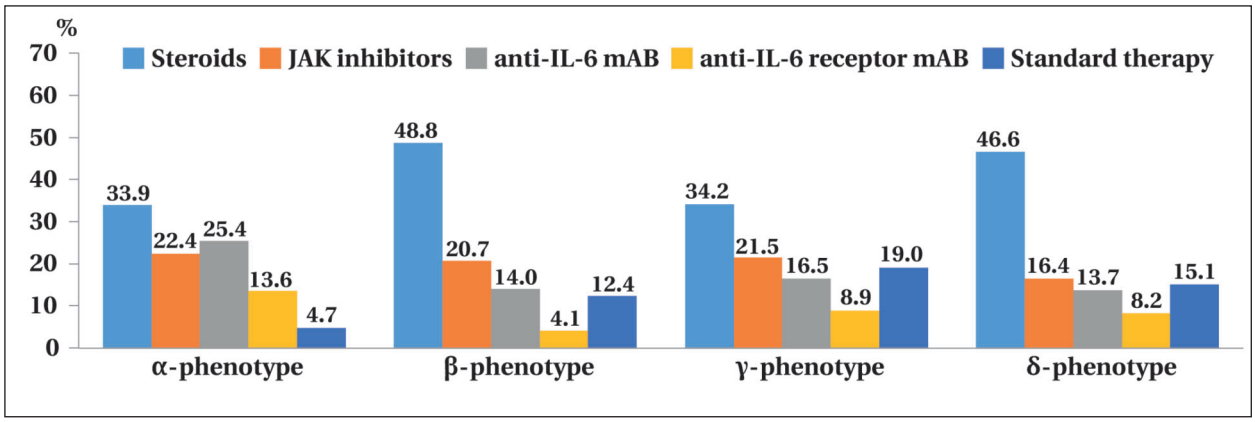

Fig. 2. Treatment of patients with COVID-19 SCAP.
Note. For Figures 2 and 3: mAB — monoclonal antibodies.

mon complication in 17 (60.7%) patients receiving BT and 23 (23.5%) patients not receiving BT (P=0.0002). Bacterial sepsis was reported significantly less frequently in patients who received BT compared to those who did not, 25.0% vs. 70.4%, respectively (P=0.0254).

The treatment of patients with COVID-19 SCAP is summarized in Fig. 2.

Patients with δ-phenotype sepsis had a lower frequency of BT: 13.7% were treated with monoclonal antibodies against interleukin-6 (mAB IL-6) and 8.2% with monoclonal antibodies against interleukin-6 receptor (mAB rIL-6). Steroid therapy (dexamethasone) was used in 46.6% of patients. BT was most frequently used in patients with α-phenotype sepsis, with 25.4% receiving IL6 mAB (olokizumab) and 13.6% receiving rIL6 mAB (tocilizumab, sarilumab).

Comparison of outcomes in α-phenotype sepsis by therapy is shown in Fig. 3.

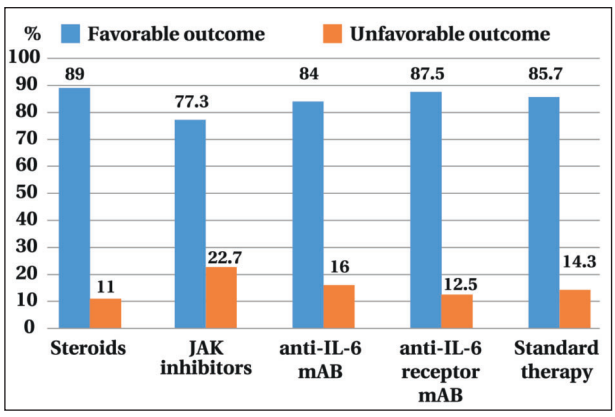

Fig. 3. Comparison of outcomes in α-phenotype sepsis by therapy.

Patients with α-phenotype sepsis who received BT (N=181, 61.8% of sample) had a higher baseline severity of illness than patients who did not receive BT (N=114, 41.5% of sample), as confirmed by severity stratification scoring systems: NEWS2 > 8 points, 172 (95.0%) vs. 110 (78.0%) (P<0.0001); A-DROP ⩾5 points, 17 (9.4%) vs. 5 (3.5%) (P=0.0376); SAPS II, 28 (24–35) vs. 26 (21.0–31.8) points (P=0.0155). Patients receiving BT had a longer ICU stay than those not receiving BT, 5 (3–9) vs. 3 (2–5) days (P<0.0001), with comparable adverse outcomes of 32 (17.7%) vs. 24 (16.9%) (P>0.05).

Bacterial sepsis was significantly less common in patients receiving BT: 12.7% of patients with BT vs. 23.2% without BT (P=0.0131).

Interleukin-6 receptor monoclonal antibody therapy was associated with a favorable outcome in 87.5% of patients with α-phenotype sepsis in the COVID-19 SCAP (P=0.0419).

A favorable outcome was also observed with the use of JAK inhibitors in 11 patients with α-, γ-, δ-phenotypes, moderate COVID-19 severity (CT-2 and NEWS=7 points) and severe comorbidities with an Elixhauser Index score of 4 (1–5).

Conclusion

We retrospectively identified four sepsis phenotypes (α — 48.6%, β — 19.3%, γ — 13.1%, δ — 19.0%) in 664 patients with viral and bacterial SCAP. We identified an association between sepsis phenotypes and SCAP progression, treatment strategies, and outcomes.

We found that the α sepsis phenotype predominated in the vSCAP group (N=295, 51.9%) and the δ-phenotype predominated in the bSCAP group (N=53, 55.2%).

We found that the frequency of BT was higher in the α-phenotype sepsis than in other phenotypes, with 61.8% in the α-phenotype, 16% in the β-phenotype, 12.6% in the γ-phenotype, and 9.6% in the δ-phenotype (P<0.05).

Patients with α- and δ-phenotypes of sepsis who received biological therapy (BT) developed

bacterial sepsis significantly less often than those who did not receive BT: in the α-phenotype 12.71% vs. 23.2% (P=0.0131), in the δ-phenotype 25.0% vs. 70.41% (P=0.0254).

In patients with α-phenotype sepsis and COVID-19 SCAP, interleukin-6 receptor monoclonal antibody therapy was associated with a favorable outcome in 87.5% of cases (P=0.0419).

Our data contribute to the development of a more differentiated approach to patient management and improve the prediction of complications and outcomes in SCAP.

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