Validation of Inflammopathic, Adaptive, and Coagulopathic Sepsis Endotypes in Coronavirus Disease 2019

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OBJECTIVES: Complex critical syndromes like sepsis and coronavirus disease 2019 may be composed of underling "endotypes," which may respond differently to treatment. The aim of this study was to test whether a previously defined bacterial sepsis endotypes classifier recapitulates the same clinical and immunological endotypes in coronavirus disease 2019.

DESIGN: Prospective single-center observational cohort study.

SETTING: Patients were enrolled in Athens, Greece, and blood was shipped to Inflammatix (Burlingame, CA) for analysis.

PATIENTS: Adult patients within 24 hours of hospital admission with coronavirus disease 2019 confirmed by polymerase chain reaction and chest radiography.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We studied 97 patients with coronavirus disease 2019, of which 50 went on to severe respiratory failure (SRF) and 16 died. We applied a previously defined 33-messenger RNA classifier to assign endotype (Inflammopathic, Adaptive, or Coagulopathic) to each patient. We tested endotype status against other clinical parameters including laboratory values, severity scores, and outcomes. Patients were assigned as Inflammopathic (29%), Adaptive (44%), or Coagulopathic (27%), similar to our prior study in bacterial sepsis. Adaptive patients had lower rates of SRF and no deaths. Coagulopathic and Inflammopathic endotypes had 42% and 18% mortality rates, respectively. The Coagulopathic group showed highest D-dimers, and the Inflammopathic group showed highest C-reactive protein and interleukin-6 levels.

CONCLUSIONS: Our predefined 33-messenger RNA endotypes classifier recapitulated immune phenotypes in viral sepsis (coronavirus disease 2019) despite its prior training and validation only in bacterial sepsis. Further work should focus on continued validation of the endotypes and their interaction with immunomodulatory therapy.

KEY WORDS: classifier; coagulopathy; coronavirus disease 2019; endotypes; sepsis

Sepsis, defined as a dysregulated immune response to an acute infection, is a highly heterogeneous syndrome (1). A complex interplay of host and pathogen dynamics leads to varying outcomes and therapy responsiveness. As a result, despite intensive searching, there remains no targeted immune modulating therapy approved for sepsis (2). One approach may be to subdivide

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patients with sepsis into separately treatable subclasses ("endotypes") using a precision-medicine approach with companion diagnostics (3). For example, perhaps there is one type of sepsis immune physiology that responds positively to corticosteroids or immune modulators, and another for which such agents may be harmful. It is anticipated that identifying such endotypes might allow for improved treatment regimes.

Coronavirus disease 2019 (COVID-19) can cause sepsis and mortality, and clearly has a heterogeneous course, with some patients being asymptomatic, others progressing quickly to acute respiratory distress syndrome and death, and some developing signs and symptoms of severe coagulopathy (4). High levels of D-dimers and prolonged prothrombin time suggest that a microvascular thrombosis may play a part in certain COVID-19 patients (5, 6).

Although observational studies suggest that patients on anticoagulation may have better outcomes from COVID-19 (7, 8), anticoagulation also leads to a higher number of severe bleeding events. We and others have shown association of certain immune modulators (e.g., interleukin [IL]-6 inhibitors and dexamethasone) with improved outcomes of patients with COVID-19 (9–11). However, overall, we lack a predictive tool to determine which COVID-19 patients may benefit from which therapies.

Although several features of COVID-19 may be different from standard viral infections, many are congruent with viral sepsis (12). Thus, existing tools for sepsis may be directly applicable in COVID-19. We previously reported the discovery and validation of three sepsis "endotypes" across 1,300 patients with bacterial sepsis at hospital or ICU admission (13). These endotypes were derived from whole blood transcriptomic data in an unsupervised approach across multiple datasets and were then linked to both clinical and molecular phenotypes (13). The endotypes were called "Inflammopathic" (high severity, high mortality, and enriched for innate immune activation), "Adaptive" (low severity, low mortality, and enriched for adaptive immune activation), and "Coagulopathic" (high severity, high mortality, and high clinical coagulopathy) (13). These endotypes have not been validated in viral patients or definitively linked to a particular therapeutic choice.

We here studied whether a previously defined 33-messenger RNA classifier for the transcriptomic endotypes score holds predictive validity in COVID-19 patients, as a first step to potentially improve therapy selection for these patients.

MATERIALS AND METHODS

As reported elsewhere (11), blood was sampled from patients with community-acquired lower respiratory tract infection by polymerase chain reaction (PCR)-confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) within the first 24 hours of hospital admission, including hospital transfers. COVID-19 infection was defined as the presence infiltrates in chest x-ray or chest CT compatible with COVID-19 and SARS-CoV-2 confirmation by positive PCR testing of respiratory secretions. For patients who required mechanical ventilation (MV), blood sampling was performed within the first 24 hours from MV and results were used for this analysis. Exclusion criteria were infection by the HIV, neutropenia, and any previous intake of immunosuppressive medication (corticosteroids, anticytokine biologicals, and biological response modifiers). The studies were conducted under the 23/12.08.2019 approval of the Ethics Committee of Sotiria Athens General Hospital; and the 26.02.2019 approval of the Ethics Committee of ATTIKON University General Hospital. Written informed consent was provided by patients or by first-degree relatives in the case of patients unable to consent.

Whole blood was drawn in PAXgene RNA tubes at enrollment along with other standard laboratory parameters. Data collection included demographic information, clinical scores (Sequential Organ Failure Assessment [SOFA] and Acute Physiology and Chronic Health Evaluation II), laboratory results, length of stay, and clinical outcomes. Labs were drawn concurrently with enrollment, and were run as part of either standard of care or post hoc for this study. Patients were followed up daily for 30 days; outcomes were defined as SRF (Pao_2/Fio_2 [P/F] ratio less than 150 requiring MV) or death. PAXgene blood RNA samples were shipped to Inflammatix, where RNA was extracted and the 33 mRNAs were quantitated using NanoString nCounter (NanoString, Seattle, WA) as described (14). Samples yielding less than 50-ng RNA were removed from the dataset.

Endotypes were calculated as previously described (13). Briefly, each of the 33 mRNAs is assigned to one of the three groups, and we calculated the difference of geometric means of gene expression for

each grouping. The groupings are: Inflammopathic: *ARG1, LCN2, LTF, OLFM4,* and *HLA-DMB*; Adaptive, *YKT6, PDE4B, TWISTNB, BTN2A2, ZBTB33, PSMB9, CAMK4, TMEM19, SLC12A7, TP53BP1, PLEKHO1, SLC25A22, FRS2, GADD45A, CD24, S100A12,* and *STX1A*; Coagulopathic, *KCNMB4, CRISP2, HTRA1, PPL, RHBDF2, ZCCHC4, YKT6, DDX6, SENP5, RAPGEF1, DTX2,* and *RELB* (note *YKT6* appears twice intentionally). We then applied the previously defined multiclass logistic regression model to these three input gene expression scores, which yields a probability of endotype assignment (for each subject, the total probability (p[Inflammopathic] + *p*[Adaptive] + *p*[Coagulopathic] sums to 1). Each sample is assigned an endotype according to the highest probability.

For coagulopathy parameters (INR, PTT, and fibrinogen were heavily missing), we calculated International Society for Thrombosis and Hemostasis (ISTH) disseminated intravascular coagulation (DIC) scores from the available data to provide a single measure of coagulopathy (15). For the ISTH DIC score, missing values were assumed normal.

Due to the relatively small sample size, we made intergroup comparisons without assumptions of normality where possible (Kruskal-Wallis rank sum or Mann-Whitney *U* test). Medians and interquartile ranges are given for continuous variables. All statistics were calculated in R Version 3.5.1 (www.r-project.org).

RESULTS

In the participating hospitals from the Hellenic Sepsis Study Group in Greece, we prospectively enrolled 100 adult patients within 24 hours of hospital admission with SARS-CoV-2 infection, of which we removed three due to low RNA yields (**Table 1**). Of the 97, a total of 50 went on to MV with SRF (P/F < 150), of which 16 died (there were no deaths in the non-SRF group). Patients progressing to mortality had higher WBCs and neutrophils, lower lymphocytes, and higher CRP, all of which are similar to other COVID-19 reports.

The previously described peripheral-blood-based 33-messenger RNA endotypes classifier was used to designate every patient as either Inflammopathic (29%), Adaptive (44%), or Coagulopathic (27%) (**Table 2**). Endotype was significantly associated with mortality, with no deaths in the Adaptive group, five deaths in the Inflammopathic group, and 11 deaths in the Coagulopathic group, in keeping with previous cohorts (13). In addition, similar to other studies, the Inflammopathic and Coagulopathic groups had older age, lower lymphocyte counts, and a higher clinical severity (as estimated by SOFA scores and need for MV). Unlike previous studies, in this cohort, the Adaptive patients had a lower WBC count and neutrophil count not previously observed. C-reactive protein has not previously been studied with the sepsis endotypes, but here was low in Adaptive, moderately induced in Coagulopathic, and highly induced in Inflammopathic patients. Similarly, IL-6 was highest in the Inflammopathic patients, and ferritin was lowest in Adaptive patients.

As some patients were enrolled after hospital transfer and so presented later in their course, we examined time since symptom onset according to respiratory failure status and endotype assignment (**Supplemental Fig. 1**, http://links.lww.com/CCM/F998). Patients with SRF were sampled further out from symptom start ($p < 0.01$), but there was no difference according to endotype assignment (analysis of variance p = not significant).

Age and clinical severity have been repeatedly reported to be associated with COVID-19 mortality and that was true here as well (Table 1). We thus sought to understand how age, SOFA score, and endotype assignment are related to mortality (**Fig. 1**). Although there is clearly an association of mortality with older age and higher SOFA, deaths still occurred in those less than 70-years old and at modest SOFA score (≤ 4). On the other hand, the Adaptive subtype had 100% survival, and the Inflammopathic and Coagulopathic endotypes were present at both extremes of age and severity.

To assign a quantitative aspect to this relationship, we examined the underlying endotype assignment probabilities, noting (as previously shown) that the classifier is very confident in Adaptive class, but less so between Inflammopathic and Coagulopathic (**Supplemental Fig. 2**, http://links.lww.com/CCM/F998). Notably, all deaths occurred in patients with near-zero probability of Adaptive endotype. Thus, we ran a multivariate regression on death as a function of age, SOFA score, and the probability of either Inflammopathic or Coagulopathic endotypes, showing significant effect from both age and endotype assignment (**Supplemental Table 1**, http://links.lww.com/CCM/F998).

TABLE 1.
Description of Cohort for All Patients and Split by Mortality Outcome

Variable	All Patients	Survivors	Deaths	*p* (Survivor vs Death)	Missing Values
n	97	81	16		
Age (yr)	62.00 (52.00–72.25)	60.00 (50.75–70.25)	68.50 (62.75–84.25)	0.003	1
Male (%)	68 (70.1)	56 (69.1)	12 (75.0)	0.865	0
WBCs	6,770 (5,145–10,227)	6,480 (5,145–9,622)	8,540 (5,542–12,510)	0.275	3
Neutrophils (%)	78.10 (68.35–86.60)	77.09 (65.22–83.75)	88.95 (86.40–93.03)	< 0.001	3
Lymphocytes (%)	12.70 (7.20–21.15)	14.03 (9.00–22.42)	6.70 (3.65–9.65)	< 0.001	3
Lymphocyte count	945.64 (664.05–1,268.78)	1,049.49 (759.72–1,395.69)	613.80 (377.93–831.28)	< 0.001	3
Platelets	215,000 (172,900–266,000)	214,000 (172,600–260,800)	249,050 (180,750–298,000)	0.176	4
D-dimers ng/mL	977.90 (476.25–2,560.00)	850.00 (437.50–1,947.50)	4,480.00 (2,440.00–13,161.50)	< 0.001	2
C-reactive protein mg/L	107.00 (31.60–222.50)	79.10 (28.80–202.00)	224.75 (142.89–260.75)	0.002	0
Interleukin-6 pg/mL	10.00 (10.00–67.00)	10.00 (10.00–59.00)	22.50 (10.00–135.00)	0.355	0
Soluble urokinase-type plasminogen activator receptor ng/mL	5.00 (3.00–6.20)	4.80 (3.00–6.00)	7.80 (5.50–9.65)	0.002	0
Ferritin ng/mL	639.0 (333.0–1,627.0)	633.0 (362.5–1,324.0)	1,407.0 (302.5–5,033.5)	0.195	8
Sequential Organ Failure Assessment score	3.00 (1.00–6.00)	2.00 (1.00–6.00)	5.00 (4.00–6.25)	0.006	1
Acute Physiology and Chronic Health Evaluation II	7.00 (5.00–11.00)	7.00 (4.00–9.00)	11.00 (8.00–13.50)	0.001	4
Bacterial superinfection at enrollment	5 (5.2)	5 (6.2)	0 (0)	0.688	0
Length of stay (d)	13.00 (11.00–20.00)	13.00 (11.00–20.00)	13.00 (8.75–17.25)	0.41	0
Mechanical ventilation (%)	50 (51.5)	34 (42.0)	16 (100.0)	<0.001	0

Continuous variables are shown as median (interquartile range).

One of the defining features of COVID-19 is the clinical coagulopathy that frequently accompanies both severe and nonsevere cases. We previously linked the Coagulopathic endotype to laboratory markers of coagulopathy (13) and so performed exploratory analysis of coagulopathy here. Since the cohort was not

TABLE 2.
Cohort Characteristics for All Patients and Broken Down by Endotype Assignment

Variable	All Patients	Inflammopathic Endotype	Adaptive Endotype	Coagulopathic Endotype	*p* (Among Endotypes)	Missing Values
n	97	28 (29%)	43 (44%)	26 (27%)		
Age (yr)	62.00 (52.00–72.25)	65.50 (55.75–74.25)	53.50 (46.50–64.00)	67.50 (60.75, 76.25)	0.001	1
Male (%)	68 (70.1)	22 (78.6)	26 (60.5)	20 (76.9)	0.179	0
WBCs	6,770 (5,145–10,227)	8,810 (6,475–12,175)	5,880 (4,850–7,300)	8,540 (5,932–10,695)	< 0.001	3
Neutrophils (%)	78.10 (68.35–86.60)	86.00 (79.00–91.25)	68.10 (54.10–75.50)	85.55 (78.65–88.00)	< 0.001	3
Lymphocytes (%)	12.70 ([7.20–21.15)	8.10 (4.00–12.00)	21.30 (14.10–29.90)	9.00 (6.60–12.07)	< 0.001	3
Lymphocyte count	945.6 (664.0–1,268.8)	757.8 (428.7–998.2)	1,203.7 (951.9–1,509.0)	797.3 (567.5–1,038.9)	< 0.001	3
D-dimers ng/mL	977.90 (476.25–2,560.00)	1,570.00 (775.00, 3,130.00)	670.00 (404.00–1,425.00)	2,400.00 (607.50–4,370.00)	0.004	2
C-reactive protein mg/L	107.00 (31.60–222.50)	222.40 (156.94–269.25)	33.80 (6.34–75.35)	166.10 (89.03–268.25)	< 0.001	0
Interleukin-6 pg/mL	10.00 (10.00–67.00)	96.00 (10.00–181.00)	10.00 (10.00–10.00)	19.00 (10.00–65.25)	< 0.001	0
Soluble urokinase-type plasminogen activator receptor ng/mL	5.00 (3.00–6.20)	5.25 (3.98–8.00)	3.00 (2.55–5.00)	6.00 (4.85–8.15)	< 0.001	0
Ferritin ng/mL	639.0 (333.0–1,627.0)	707.0 (480.0–2,187.0)	570.0 (199.5–952.0)	1,018.0 (496.0–2,472.0)	0.027	8
Sequential Organ Failure Assessment score	3.00 (1.00–6.00)	5.00 (3.00–7.00)	2.00 (1.00–2.00)	6.00 (3.00–7.00)	< 0.001	1
Acute Physiology and Chronic Health Evaluation II	7.00 (5.00–11.00)	10.00 (6.50–12.00)	4.00 (3.00–7.00)	8.00 (7.00–13.00)	< 0.001	4
Bacterial superinfection at enrollment	5 (5.2)	2 (7.1)	2 (4.7)	1 (3.8)	0.844	0
Length of stay (d)	13.00 (11.00–20.00)	19.00 (12.00–27.25)	12.00 (10.50–14.00)	14.00 (11.00–20.75)	0.002	0
Mechanical ventilation	50 (51.5)	21 (75.0)	8 (18.6)	21 (80.8)	< 0.001	0
Death (%)	16 (16.5)	5 (17.9)	0 (0.0)	11 (42.3)	< 0.001	0

Continuous variables are shown as median (interquartile range).

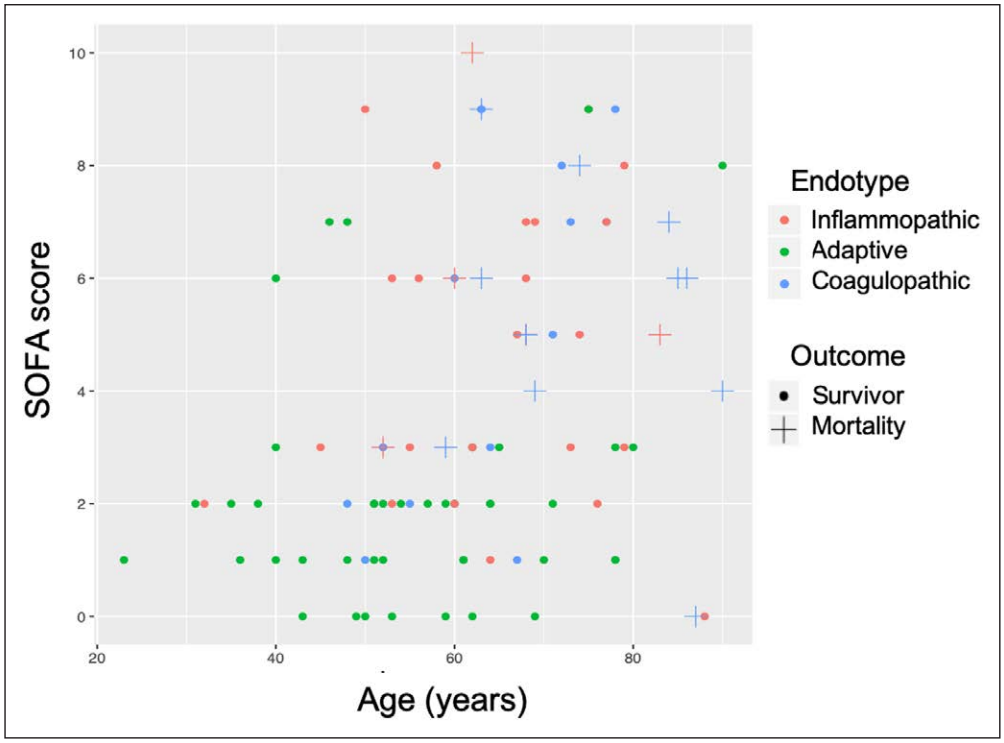

Figure 1. Death as a function of age, clinical severity, and endotype assignment. *x*-axis shows age in yr, *y*-axis shows Sequential Organ Failure Assessment (SOFA) score. *Color* shows endotype assignment and *shape* shows outcome (30-d inhospital death). There is a complex relationship among age, clinical severity (SOFA), and endotype assignment in predicting death.

prospectively enrolled to study coagulopathy, there was some missingness in the coagulopathy variables (INR, PTT, and fibrinogen). We observed significant differences in PTT, fibrinogen, D-dimers, and ISTH DIC scores across the endotypes (**Table 3**). Furthermore, among these 97 patients, there were nine thromboembolic events (deep-vein thrombosis, stroke, or pulmonary embolus) ranging from 5 to 88 days after enrollment, and these were not significantly different among endotypes. There were no clinical diagnoses of DIC. More work is needed to understand the relationship between coagulopathy in COVID-19 and the three endotypes.

We plotted endotypes against IL-6 as a marker of overall inflammation and D-dimers as a marker of coagulopathy (**Fig. 2*A***). Subjects with both D-dimers and IL-6 generally grouped as follows: low D-dimer/low IL-6: Adaptive; high D-dimer/low IL-6: Coagulopathic; low D-dimer/high IL-6: Inflammopathic. Interestingly, no high D-dimer/high IL-6 subjects were observed. Evaluating the underlying probabilities of endotype assignment rather than the categorical class, we found that Inflammopathic probability is positively associated with IL-6 levels, and Coagulopathic endotype probability is positively associated with D-dimer presence (**Fig. 2**, *B* or *C*).

DISCUSSION

We show here that previously defined transcriptomic endotypes discovered and validated in bacterial sepsis ($n = 1{,}300$ from 23 cohorts) (13) appear to be present in patients with COVID-19. We used a preset 33-messenger RNA classifier to calculate the endotypes blinded to clinical outcomes, further emphasizing the validity of the experimental framework. The Inflammopathic, Adaptive, and Coagulopathic endotypes continue to show significant association with clinical outcomes in a manner similar to their initial discovery. We observed high mortality in the Inflammopathic and Coagulopathic groups, with Inflammopathic showing high traditional inflammatory markers and Coagulopathic showing disruption in markers of coagulopathy (but not an association with thromboembolic events). The patients also assigned to classes at comparable rates to prior studies (here 29%, 44%, and 27% Inflammopathic, Adaptive, and Coagulopathic, respectively; prior total rate was 35%, 44%, and 21%). Notably, these findings were present in patients with acute viral infections/sepsis, rather than bacterial infections/sepsis. This suggests that the host response of clinical "sepsis" (however it is defined) may have commonalities across infection types, despite known different host responses to different infection types. Furthermore, COVID-19 has been described as inducing a "cytokine storm" (16, 17), but we prefer to classify it as "viral sepsis." This study suggests that some molecular features of the COVID-19 host response are similar to bacterial sepsis.

Although the sepsis endotypes do show prognostic capacity in terms of outcomes, we reemphasize that purpose-built tools for prognosis of mortality are

TABLE 3.
Coagulation Parameters for All Patients and Broken Down by Endotypes

Variable	All Patients	Inflammopathic Endotype	Adaptive Endotype	Coagulopathic Endotype	*p* (Among Endotypes)	Missing Values
n	97	28	43	26		
Platelets	215,000 (172,900–266,000)	220,000 (181,500–295,000)	205,000 (159,050–243,000)	224,500 (174,450–285,650)	0.357	4
International normalized ratio	1.09 (1.03–1.23)	1.11 (1.03–1.19)	1.07 (0.98–1.15)	1.20 (1.06–1.29)	0.065	16
Activated partial thromboplastin time	34.53 (30.43–39.98)	37.40 (32.80–40.20)	31.30 (30.10–38.10)	36.60 (30.77–41.75)	0.046	19
Fibrinogen mg/dL	500.00 (371.00–707.00)	604.00 (420.00–767.00)	385.50 (339.10–569.00)	674.00 (532.00–775.00)	0.001	38
D-dimers ng/mL	977.90 (476.25–2,560.00)	1,570.00 (775.00–3,130.00)	670.00 (404.00–1,425.00)	2,400.00 (607.50–4,370.00)	0.004	2
ISTH DIC score	0 (0–2)	0 (0–2)	0 (0–0)	2 (0–2.75)	0.001	0
ISTH DIC score ≥ 3 (%)	4 (4.1)	1 (3.6)	1 (2.3)	2 (7.7)	0.546	0
Clinical DIC	0	0	0	0	NA	0
Thromboembolic events (%)	9 (9.3)	5 (17.9)	2 (4.7)	2 (7.7)	0.164	0

DIC = disseminated intravascular coagulation, ISTH = International Society of Thrombosis and Hemostasis.
Many parameters are heavily missing (see right).

probably better suited to this clinical task. Sepsis is a highly heterogeneous syndrome that has withstood all attempts at immunomodulatory therapy, and the promise of "lumping and splitting" in critical illness syndromes is the identification of differently treatable patient subgroups and an elucidation of underlying biology (3). It is possible that our endotype molecular classifier could identify patients with different pathophysiologies matched to targeted therapeutic intervention. For instance, if confirmed in further studies, it is possible that "Inflammopathic" and "Coagulopathic" subgroups may benefit from blockade of typical proinflammatory cytokines (e.g., IL-1 or IL-6) (9, 10) or early anticoagulation (7, 8). Since the endotypes appear to be present both in bacterial sepsis and in COVID-19, the immunomodulatory approach may be broadly applicable to patients with the same endotype despite their different underlying pathogenic origins. Certainly, this study is hypothesis-generating only. If confirmed with future studies, the 33-messenger RNA classifier could be used as a companion-diagnostic test to guide a precision-medicine-based intervention; Inflammatix is developing a rapid diagnostic platform that could measure the endotypes at the point of care in 30 minutes.

From a broader perspective, the 33-messenger RNA sepsis endotypes classifier is one of several transcriptomic classifiers that purport to divide critically ill patients into useful subtypes (18–22). We did not test the other classifiers here so cannot comment on their similarity or difference. It is possible that the classifiers could all be true but differently useful; perhaps, for example, a patient could be both "Endotype B" as described by Wong et al (19) and "Coagulopathic," suggesting both corticosteroids and anticoagulants (23). Such hypotheses are the subject of ongoing work.

We also note that other immunoprofiling efforts in COVID-19 have similarly found heterogeneous clinical

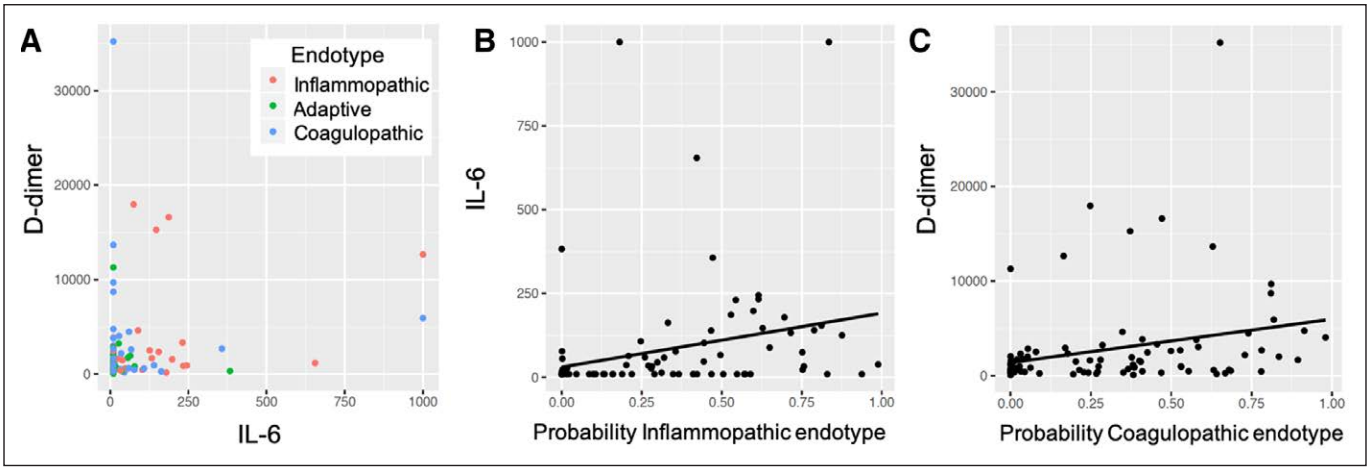

Figure 2. A, Relationship between endotypes, D-dimers, and interleukin (IL)-6. **B**, IL-6 as a function of Inflammopathic probabilities. The linear regression shows R-squared = 0.08, $p < 0.01$. **C**, D-dimer as a function of Coagulopathic endotype probabilities. The linear regression shows R-squared = 0.07; $p < 0.01$.

phenotypes and immune markers among ICU patients (24–26). For instance, Laing et al (26) note that of ICU patients with COVID-19, only a subset of persistent "hyperinflammatory" patients have high ferritin, high procalcitonin, and high D-dimers. Thus, "hyperinflammatory" patients may represent a mix of Inflammopathic/Coagulopathic patients. The overlap with other immune profiles in COVID-19 remains an area of future studies.

Our study has some limitations, notably a small sample size from a single center and some missing clinical data from the coagulation laboratory parameters. Furthermore, we included patients at different time points in their clinical trajectory, and the study did not account for interventions such as steroids, anticoagulants, antivirals, and other novel therapies for COVID-19. On the other hand, we used a preset tool (33-messenger RNA classifier) and validated preset clinical findings previously shown to be associated with the endotypes, lending credence to the findings.

CONCLUSIONS

Overall, we suggest that the heterogeneity of sepsis is also present in COVID-19. The 33-messenger RNA classifier is one possible way to reduce the clinical heterogeneity and potentially inform therapeutic decisions. We suggest that future studies of immunomodulatory therapy in sepsis or COVID-19 should at least draw RNA-stabilized blood at the time of enrollment such that a retrospective endotypes analysis (using ours or other classifiers) can be performed. For instance, given the recent association of decreased COVID-19 mortality with dexamethasone (27), it would be interesting to examine differential benefits according to endotype. It is only through such retrospective analyses that we will gain the confidence to apply the endotypes in interventional treatment randomization. More work is needed to identify and confirm a companion-diagnostic approach to immunomodulatory therapy in COVID-19 and sepsis.

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Drs. Sweeney, Liesenfeld, and Giamarellos-Bourboulis designed the study. Drs. Kotsaki, Kanavou, Leventogiannis, Kontogeorgou, and Giamarellos-Bourboulis conducted the clinical study. Drs. Sweeney and Wacker performed statistical analysis. Dr. Rawling, Dr. Remmel, Ms. Coyle, and Dr. Midic performed clinical sample and data processing. Dr. Sweeney wrote the initial manuscript draft. All authors critically reviewed.

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