Thromboembolic phenomena are an important complication of infection by severe acute respiratory coronavirus 2 (SARS-CoV-2). Increasing focus on the management of the thrombotic complications of Coronavirus Disease 2019 (COVID-19) has led to further investigation into the role of platelets, and their precursor cell, the megakaryocyte, during the disease course. Previously published postmortem evaluations of patients who succumbed to COVID-19 have reported the presence of megakaryocytes in the cardiac microvasculature. Our series evaluated a cohort of autopsies performed on SARS-CoV-2-positive patients in 2020 ($n = 36$) and prepandemic autopsies performed in early 2020 ($n = 12$) and selected to represent comorbidities common in cases of severe COVID-19, in addition to infectious and noninfectious pulmonary disease and thromboembolic phenomena. Cases were assessed for the presence of cardiac megakaryocytes and correlated with the presence of pulmonary emboli and laboratory platelet parameters and inflammatory markers. Cardiac megakaryocytes were detected in 64% (23/36) of COVID-19 autopsies, and 40% (5/12) prepandemic autopsies, with averages of 1.77 and 0.84 megakaryocytes per cm$^2$, respectively. Within the COVID-19 cohort, autopsies with detected megakaryocytes had significantly higher platelet counts compared with cases throughout; other platelet parameters were not statistically significant between groups. Although studies have supported a role of platelets and megakaryocytes in the response to viral infections, including SARS-CoV-2, our findings suggest cardiac megakaryocytes may be representative of a nonspecific inflammatory response and are frequent in, but not exclusive to, COVID-19 autopsies.

Keywords: COVID-19, megakaryocytes, platelets, SARS-CoV-2
multiorgan failure and death in severe cases.  

Severe COVID-19 is associated with a robust inflammatory response with immune dysfunction, including cytokine release syndrome (CRS), which contributes to pulmonary pathology and development of ARDS.  

The immune response to SARS-CoV-2 is dynamic, and differs between patients with mild and severe infections.  

Laboratory findings in severe COVID-19 include elevations in inflammatory cytokines, including tumor necrosis factor-α (TNF-α), and interleukins (IL), including IL-1, IL-6, IL-8, IL-18, and other inflammatory markers including C-reactive protein (CRP), D-dimer, and fibrinogen.  

Elevations in inflammatory cytokines and D-dimer have been associated with critical illness and mortality.  

Other laboratory findings in severe COVID-19 include prolonged prothrombin and activated partial thromboplastin time, lymphopenia, and variably, thrombocytopenia.  

Although initial reports emphasized the respiratory dysfunction associated with severe COVID-19 infection, thromboembolic phenomena were quickly recognized as a common and significant complication of COVID-19.  

Thrombosis has been reported in 30–40% of patients hospitalized with COVID-19, and pulmonary embolism is the most common reported complication.  

Macroscopic thrombosis and microthrombi are reported in ~20% and 50% of autopsies, respectively.  

Histologic examination of lungs from patients who died from COVID-19 frequently demonstrate thrombotic phenomena, including venous thromboemboli as well as capillary microthrombi, at an increased prevalence compared to other respiratory viruses such as influenza and SARS-CoV.  

Notably, procoagulation abnormalities have also been described in SARS and MERS.  

Increasing focus on the management of the thrombotic complications of COVID-19 has led to investigations into the role of platelets, and their precursor cell, the megakaryocyte, during the disease course.  

In addition to their well-described contribution to thrombosis, platelets also play diverse roles in innate and adaptive immunity and act as inflammatory effectors in processes such as atherosclerosis.  

Platelet count, size, and immaturity are associated with critical illness and all-cause mortality in COVID-19.  

Platelet activation occurs in inflammatory states, including viral infection, and contributes to the development of ARDS.  

Enhanced platelet activation has been previously studied in other respiratory viral infections.  

Platelets have been demonstrated to internalize other viral particles, including human immunodeficiency virus (HIV), hepatitis C virus, and dengue with resultant platelet activation and demonstrable degranulation with release of complement (C3).  

COVID-19 is associated with alteration of platelet number, size and function, include hyperactivity and increased aggregation, and increased thromboxane generation.  

Alterations in platelet activation have been described in patients with severe infection, and increased activation has been associated with poorer patient outcomes, including thrombosis or death.  

Megakaryocytes, the precursor cell of platelets, are normally present in human bone marrow and lungs and shed platelets into circulation.  

Pulmonary megakaryocytes are hypothesized to play a role in platelet homeostasis, although their contribution to overall platelet production is unclear.  

Increased pulmonary megakaryocytes have been previously reported in conditions such as diffuse alveolar damage, sepsis, and shock.  

Platelets produced by pulmonary megakaryocytes are active contributors to alveolar damage and repair responses in Diffuse alveolar damage (DAD).  

There are numerous reports of increased pulmonary megakaryocytes in COVID-19.  

Curiously, in addition to the lung, megakaryocytes have also been identified postmortem in cardiac tissue of COVID-19 patients.  

Typical acute cardiac findings in COVID-19 autopsies attributable myocardial infarction and early ischemic injury, mural fibrin thrombi, and mild epicardial inflammation.  

Commonly, manifestations of chronic cardiac disease are identified, including myocardial hypertrophy, coronary atherosclerosis, and focal myocardial fibrosis.  

Despite interest in cardiac findings in COVID-19 based on early reports of myocarditis, which have not been supported by subsequent autopsy series, review of the autopsy literature does not reveal widespread reporting of this subtle finding in COVID-19 cases.  

Rapkiewicz et al. reported the presence of megakaryocytes in the cardiac microvasculature in seven of seven cases, and Tombolini et al. reported in two of two cases.  

However, there have been no large series investigating whether this is exclusive to covid infection or seen in other inflammatory processes.  

In our series, we examined cardiac tissue obtained from 36 consecutive autopsies of COVID-19 patients performed at our institution to identify the presence of megakaryocytes in microvasculature.  

Additionally, we examined cardiac tissue from 12 control, non-COVID cases performed prior to the start of the COVID-19 pandemic.  

These cases were selected following retrospective review of finalized autopsy reports to represent nonspecific histopathologic findings overlapping with features of COVID-19, including diffuse alveolar damage or thromboemboli and comorbidities frequently associated with severe...
COVID-19, including atherosclerotic and ischemic heart disease or immunosuppression (see summary tables for clinical information).

### Materials and Methods

**Patient Samples**

This study was performed with the approval of the Institutional Review Board at Brigham and Women’s Hospital. Cases were retrieved from the Anatomic Pathology files of Brigham and Women’s Hospital and included 36 patients with laboratory-confirmed COVID-19 who underwent autopsy between April–June 2020, and 12 patients who underwent autopsy pre-COVID-19 pandemic between January–April 2020. Prepandemic control cases were selected to include causes of death overlapping with features of severe COVID-19 (including thromboemboli or pulmonary embolus \([n = 4]\), diffuse alveolar damage \([n = 2]\), bronchopneumonia \([n = 2]\)), or based on pre-existing conditions (atherosclerotic coronary artery disease and/or ischemic heart disease \([n = 3]\), interstitial lung disease \([n = 2]\), metastatic carcinoma \([n = 1]\)). Of the COVID-19 patients, 32 (88.89%) patients had tested positive for SARS-CoV-2 by RT-PCR of nasopharyngeal swabs in a CLIA-certified laboratory during hospital admission, and the remainder were positive by serology (IgG).

The electronic medical record was searched in all cases for medical comorbidities, admission status (ICU or non-ICU), SARS-CoV-2 detection methodology, antiplatelet medications, and use of extracorporeal membrane oxygenation. Available premortem laboratory values, including the latest documented result within 1 week of the patient’s death, were evaluated, including platelet counts, mean platelet volume (MPV), prothrombin time (PT), partial thromboplastin time (PTT), C-reactive protein (CRP), D-dimer, fibrinogen, and IL-6 were assessed.

All patients underwent unrestricted autopsy with complete anatomic dissection, except for patients 14, 44, and 45 in whom the brain was excluded from the autopsy permission. The presence of gross pulmonary emboli and microthrombi at autopsy were reported. Hematoxylin and eosin-stained histologic sections were reviewed by multiple surgical pathologists (R.F.P., K.L.G.). Histologic descriptions for control autopsies were recorded from finalized autopsy reports. IHC was performed on a single representative block from each case, consisting of left and/or right ventricle, using a modified protocol described by Klairmont et al.\(^4^5\) Staining for CD42b was performed on a BOND III Immunostainer (Leica Biosystems, Buffalo Grove, IL, USA). Pretreatment (heat-induced epitope retrieval) at low pH (ER1: Leica Biosystems) was performed for 30 min, followed by incubation with anti-human CD42b rabbit monoclonal antibody (clone SP219; ABCAM, Waltham, MA, USA), diluted 1:1000 for 1 h. Detection was performed using DAB Refine Polymer Detection Kit (Leica Biosystems). Slides were then briefly immersed in dilute copper sulfate solution, counterstained, dehydrated through solvents, and coverslipped. IHC stains were reviewed for the presence of megakaryocytes by three surgical pathologists (K.L.G., R.F.P., O.P.). Reviewing pathologists were not blinded to the COVID-19 status of the decedent. Megakaryocytes were enumerated in each slide. To account for differences in sampling, tissue present on each slide was individually measured to express the number of megakaryocytes present per cm\(^2\).

**Statistical Analyses**

Laboratory results were compared between COVID-19-positive and COVID-19-negative cohorts, cases with and without detectable cardiac megakaryocytes between cohorts and within the same autopsy cohorts. The raw number of megakaryocytes detected and number of megakaryocytes per cm\(^2\) was compared between COVID-19-positive and egative autopsies. Statistical analysis performed with GraphPad Prism software (San Diego, CA, USA) included unpaired two-tailed T-test and Fisher’s test.

### Results

**Clinicopathologic Data**

Clinicopathologic data in 36 patients with COVID-19 and 12 patients without COVID-19 are summarized in Table 1. In the COVID-19-positive cohort, 14 female and 21 male decedents with an average age of 68.1 years (range, 43–96 years), were assessed. In the control prepandemic group, three females and nine males, with an average age of 68.2 years (range, 54–77 years), were assessed. Documented antiplatelet therapies included aspirin (6/12 control [50.00%], 4/36 COVID-19 [11.11%]) and clopidogrel...
| Case # | Age | Sex | Status | ECMO | Cause of Death | Autoimmune/Inflammatory | Neoplastic | Cardiopulmonary / Vascular | Antiplalet Medication | Anticoagulation |
|--------|-----|-----|--------|------|----------------|-------------------------|------------|---------------------------|---------------------|-----------------|
| 1      | 70  | F   | non-ICU| No   | Pulmonary embolus | Remote h/o thyroid cancer | Thyroid carcinoma (remote) | –            | –                       | –                   | –               |
| 2      | 54  | M   | ICU    | No   | Pulmonary embolus | Lung transplant status    | Non-Hodgkin lymphoma      | Cystic fibrosis | –                       | Apixaban, Heparin   |
| 3      | 64  | F   | ICU    | No   | Usual interstitial pneumonia | Lung transplant status | –                      | Usual interstitial pneumonia, CAD | –                   | Heparin          |
| 4      | 76  | F   | non-ICU| No   | Pulmonary embolus | –                        | –                      | COPD          | Aspirin                 | –                   |
| 5      | 76  | M   | ICU    | Yes  | Atherosclerotic coronary artery disease | –                        | Colorectal carcinoma (remote) | –            | Aspirin, Heparin         |
| 6      | 71  | M   | ICU    | No   | Usual interstitial pneumonia with diffuse alveolar damage | –                        | –                      | CAD, valvular heart disease | Aspirin          | Enoxaparin       |
| 7      | 77  | M   | ICU    | No   | Bronchopneumonia in the setting of coronary artery disease | –                        | Metastatic GI small cell neuroendocrine carcinoma | CKD          | –                   | –               |
| 8      | 64  | M   | ICU    | No   | Multisystem organ failure due to thromboembolus | –                        | –                      | Flu-like illness (COVID -) | –                   | –               |
| 9      | 71  | M   | non-ICU| No   | Metastatic oral squamous cell carcinoma | –                        | –                      | CAD, IVC thrombus | –                   | Rivaroxaban       |
| 10     | 55  | M   | ICU    | No   | Atherosclerotic coronary artery disease and ischemic heart disease | –                        | –                      | Flu-like illness (COVID -), ERSD, DM | Aspirin          | Bivalirudin     |
| 11     | 65  | M   | ICU    | No   | Diffuse alveolar damage | Metastatic adenocarcinoma of unknown primary | –                      | UIP, HCM       | Aspirin              | –                   |
| Case # | Age  | Sex | Status | ECMO | Cause of Death | Autoimmune/Inflammatory | Neoplastic | Cardiopulmonary / Vascular | Antiplatelet Medication | Anticoagulation |
|--------|------|-----|--------|------|----------------|-------------------------|------------|---------------------------|------------------------|------------------|
| 12     | 76   | M   | ICU    | No   | Bronchopneumonia | –                       | Incidental prostatic adenocarcinoma | HTN, CKD     | Aspirin                  | Heparin               |
| 13     | 57   | M   | non-ICU| No   | PCR 0          | COVID-19 pneumonia with DAD | –          | DM HTN Neurologic impairment | None                  | None              |
| 14     | 68   | F   | ICU    | No   | PCR 1          | COVID-19 pneumonia       | Febrile neutropenia       | CAD COPD DM HTN     | Clopidogrel            | None              |
| 15     | 90   | M   | non-ICU| No   | PCR 9          | COVID-19 pneumonia with DAD | –          | Prostatic adenocarcinoma | CKD DM HTN Stroke Dementia | None              |
| 16     | 77   | M   | ICU    | No   | PCR 3          | COVID-19 infection with superimposed bacterial pneumonia | –          | CKD DM                  | –                     | Heparin           |
| 17     | 58   | M   | ICU    | No   | PCR 2          | COVID-19 pneumonia       | –          | CF HTN Stroke Neurologic impairment | Aspirin               | Heparin           |
| 18     | 54   | F   | ICU    | No   | PCR 6          | COVID-19 pneumonia       | Anaplastic astrocytoma   | Hemiplegia Stroke | None                  | Enoxaparin           |
| 19     | 53   | M   | ICU    | No   | PCR 18         | COVID-19 pneumonia       | –          | CKD DM HTN               | Aspirin               | Heparin           |
| 20     | 90   | M   | non-ICU| No   | PCR 6          | COVID-19 pneumonia       | –          | DM HTN                  | None                  | None              |
| 21     | 48   | M   | ICU    | No   | PCR 0          | COVID-19 pneumonia       | –          | Atherosclerosis           | None                  | None              |
| Case # | Age | Sex | Status | ECMO | SARS-CoV-2 detection method | Interval between SARS-CoV-2 test detection and death | Cause of Death | Autoimmune/Inflammatory | Neoplastic | Cardiopulmonary/Vascular | Antiplatelet medication | Anticoagulation |
|--------|-----|-----|--------|------|-----------------------------|-----------------------------------------------|---------------|-------------------------|-----------|-------------------------|------------------------|-----------------|
| 22     | 53  | M   | ICU    | No   | PCR                         | 5                                             | COVID-19 pneumonia with DAD                   | -            | -                      | -         | Acute bacterial pneumonia; OSA | None                  | Heparin         |
| 23     | 69  | F   | ICU    | No   | PCR                         | 24                                            | COVID-19 pneumonia                           | -            | -                      | -         | CAD COPD DM HTN Stroke               | Aspirin            | Heparin         |
| 24     | 76  | M   | ICU    | No   | PCR                         | 7                                             | COVID-19 pneumonia                           | -            | Non-Hodgkin lymphoma    | -         | CAD CHF CKD DM OSA                    | None                | Apixaban, heparin |
| 25     | 49  | F   | ICU    | No   | PCR                         | 9                                             | COVID-19 pneumonia (polysubstance abuse)      | -            | -                      | -         | None                                | Enoxaparin, heparin |
| 26     | 77  | M   | ICU    | No   | PCR                         | 25                                            | COVID-19 pneumonia                           | Rheumatoid arthritis                         | -          | HTN                                 | None                | Enoxaparin       |
| 27     | 57  | M   | ICU    | No   | PCR                         | 31                                            | COVID-19 pneumonia                           | -            | -                      | HTN      | None                                | Enoxaparin           |
| 28     | 96  | F   | non-ICU| No   | PCR                         | 11                                            | Aortic atherosclerosis-is with intestinal necrosis in setting of Acute MI | -          | -                      | DVT HTN Stroke with neurologic impairment | None                | Enoxaparin       |
| 29     | 63  | M   | ICU    | No   | PCR                         | 18                                            | COVID-19 pneumonia                           | -            | -                      | DM HTN   | None                                | Heparin              |
| 30     | 66  | F   | ICU    | No   | Serology                    | 1                                             | Gastrointestinal stromal tumor                | SLE        | GIST                   | Acute aspiration pneumonia; Cardiomegaly DM HTN | None                | Heparin         |
| 31     | 66  | F   | ICU    | No   | PCR                         | 34                                            | COVID-19 pneumonia                           | -            | -                      | Asthma CAD COPD HTN               | None                | Enoxaparin       |
| 32     | 82  | F   | non-ICU| No   | PCR                         | 8                                             | COVID-19 pneumonia                           | -            | -                      | CAD CHF CKD DM HTN               | None                | None           |
| Case # | Age | Sex | Status | ECMO | SARS-CoV-2 detection method | Interval between SARS-CoV-2 test detection and death | Cause of Death | Autoimmune/Inflammatory | Neoplastic | Cardiopulmonary/Vascular | Antiplatelet medication | Anticoagulation |
|--------|-----|-----|--------|------|-----------------------------|------------------------------------------------|---------------|------------------------|------------|------------------------|------------------------|-----------------|
| 33     | 80  | F   | ICU    | No   | PCR                         | 44                                            | Multisystem organ failure | –                      | –                      | DVT HTN Neurologic impairment | None                  | Enoxaparin, heparin |
| 34     | 75  | M   | non-ICU| No   | PCR                         | 2                                             | Lung squamous cell carcinoma | –                      | Lung squamous cell carcinoma | HTN                    | None                  | Enoxaparin         |
| 35     | 43  | M   | ICU    | No   | PCR                         | 33                                            | COVID-19 pneumonia        | Common variable immunodeficiency | –                      | Asthma Bronchiectasis  | None                  | None              |
| 36     | 66  | F   | ICU    | No   | PCR                         | 7                                             | COVID-19 pneumonia        | SLE Rheumatoid arthritis Pulmonary fibrosis CKD Interstitial lung disease MGUS | –                      | CAD HTN                | None                  | Heparin            |
| 37     | 50  | M   | ICU    | No   | PCR                         | 8                                             | COVID-19 pneumonia        | Urinary tract infection Aspergillus pneumonia | B-ALL                 | None                   | None                  | None              |
| 38     | 70  | M   | non-ICU| No   | PCR                         | 0                                             | Pulmonary Embolus in setting of COVID-19 | –                      | –                      | Atherosclerosis DM    | None                  | None              |
| 39     | 81  | M   | non-ICU| No   | PCR                         | Unknown                                       | COVID-19 pneumonia        | –                      | –                      | HTN OSA Dementia       | None                  | None              |
| 40     | 66  | M   | ICU    | No   | PCR                         | 16                                            | COVID-19 pneumonia        | –                      | –                      | Atherosclerosis CAD COPD DM HTN | None                  | Heparin            |
| 41     | 48  | M   | ICU    | No   | PCR                         | 6                                             | Gallbladder perforation   | –                      | –                      | Liver cirrhosis DM     | None                  | Heparin            |
| Case # | Age | Sex | Status | ECMO | SARS-CoV-2 detection method | Interval between SARS-CoV-2 test detection and death | Cause of Death | Autoimmune/Inflammatory | Neoplastic | Cardiopulmonary/Vascular | Antiplatelet medication | Anticoagulation |
|--------|-----|-----|--------|------|----------------------------|--------------------------------------------------|---------------|------------------------|------------|------------------------|------------------------|---------------|
| 42     | 91  | F   | non-ICU| No   | PCR                        | Unknown                                          | Coronary atherosclerotic disease and ischemic heart disease | –           | –                      | DM HTN Dementia       | None          | None          |
| 43     | 45  | M   | ICU    | Yes  | PCR                        | 24                                               | COVID-19 pneumonia                                        | –           | –                      | HTN Neurologic impairment | None          | Heparin        |
| 44     | 76  | F   | non-ICU| No   | PCR                        | 22                                               | Acute Myeloid Leukemia AML EBV viremia                  | –           | –                      | DVT HTN Neurologic impairment | None          | Heparin        |
| 45     | 80  | F   | ICU    | No   | PCR                        | 44                                               | COVID-19 leading to multisystem organ failure          | –           | –                      | DVT HTN Neurologic impairment | None          | Enoxaparin    |
| 46     | 86  | M   | ICU    | No   | PCR                        | 21                                               | Systemic amyloidosis Prostatic adenocarcinoma Rectal adenocarcinoma Cardiac amyloidosis with CHF CKD DM HTN | –           | –                      | Aspirin Heparin         |               |               |
| 47     | 80  | M   | non-ICU| No   | PCR                        | Unknown                                          | Neurodegenerative disease                              | –           | –                      | Dementia HTN Neurologic impairment |               |               |

| None | None | 48  | 66  | F   | ICU  | No   | Serology | 4 | COVID-19 pneumonia |

Aplastic Anemia – None None
use in one COVID-19 patient (1/36, 2.78%). Anticoagu- 
ation, including active outpatient and inpatient medications, was documented in seven control (7/12, 
58.33%) and 24 COVID-19 (24/36, 66.67%) cases 
(Table 1). Twenty-five (25/36, 69%) of COVID-19 patients were admitted to the ICU and one underwent Extracorporeal membrane oxygenation (ECMO), com-
pared with nine (9/12, 75%) of the prepandemic patients. No prepandemic patients underwent ECMO. 
The average interval between SARS-CoV-2 detection and death was 13.6 days (range, 0–44 days).

LABORATORY DATA
Premortem laboratory results for control and COVID-
19 patients are summarized in Table 2. Average values are provided when adequate data are available, 
with exclusion of laboratory results outside of the assay’s quantifiable range (reported as multiple of upper limit of normal). In the COVID-19-positive cohort, average laboratory values were as follows: platelet count = 237.1 K/µl (range, 37–642), MPV = 10.99 fl (range, 9.2–13.2), CRP = 109.0 mg/l (range, 6.1 – >300), fibrinogen = 514.1 mg/dl (range, < 60–758), IL-6 = 152.8 pg/ml (range, 8.1 – >400), PT = 20.8 sec (range, 12.6–64.4), PTT = 44.7 sec (range, 13.5 – >150).

In the prepandemic cohort, average laboratory values were as follows: platelet count = 250.5 K/µl (range, 77–520), MPV = 11.29 fl (range, 9.9–11.8), CRP = 60.2 mg/l (range, 8.3–144.1), fibrinogen = 464.2 mg/dl (range, 203–602), PT = 23.5 sec (range, 13.0–37.5), PTT = 67.8 sec (range, 29.8–138.3). D-dimer levels, expressed as multiples of the upper limit of normal, averaged 6.19 in the COVID-19 cohort (range, 1.5–10) and 7.00 in the prepan-
demic cohort (range, 4–8). An IL-6 measurement was only documented in one prepandemic case, with a value of 69.6 pg/ml.

Platelet parameters, including platelet count, MPV, CRP, fibrinogen, IL-6, d-dimer, PT, PTT values were reflective of inflammatory states and comparable between SARS-CoV-2 and prepandemic cohorts, with no statistically significant differences as described above. Troponin values approached statistical significance, and were higher in the statisti-

cal cohort, with an average of 829.5 ng/l in the prepandemic cohort compared to 44.7 ng/l in the COVI

D-19-positive cases (P = 0.0054; difference between means and SEM = 784.8 ± 258.2). This result is likely reflective of intentional selection of cases with cardiac comorbidities for the non-COVID cohort.

AUTOPSY FINDINGS
The postmortem interval was 1–2 days in all cases. Causes of death are summarized in Table 1. Pulmonary thromboemboli were documented in 67% of COVID-19 cases (24/36 cases) compared with 50% of preCOVID control cases (6/12 cases), P = 0.3250. There was no correlation between antiplatelet ther-

apy and the presence of thromboemboli (correlation coefficient = −0.04957). There was no relationship between platelet count and antiplatelet therapy in either cohort (in the COVID+ cohort, P = 0.8916; in prepandemic autopsies, P = 0.8875).

Gross and histologic cardiac findings frequently included manifestations of chronic disease (Table 3). Most frequent gross findings included cardiomegaly and/or ventricular hypertrophy and dilation in 55% of COVID-19 cases (20/36) and 50% of prepandemic cases (6/12), CAD in 55% of COVID-19 cases (20/ 
36), and 42% of prepandemic cases (5/12). Histologic findings included at least moderate myocyte hypertrophy documented in 5% of COVID-19 cases (2/36) and 42% of prepandemic cases (5/12). Acute ischemic changes, including myocardial infarction and microinfarction, were identified in 22% of COVID-19 cases (8/36) and 42% of prepandemic cases (5/12). Myocarditis was reported in one COVID-
19 patient.

CARDIAC MEGAKARYOCYTES
Megakaryocytes were detected by CD42b IHC in the cardiac microvasculature of 23 (64%) of cases in our COVID-19 autopsy series (see Figure 1A, Table 3). An average of 5.8 megakaryocytes were detected per section, or 1.77 megakaryocytes per cm². The average age of COVID-19 cases with megakaryocytes was 67.2 years, compared with 69.6 years in the remaining cases. The interval between SARS-CoV-2 detection and death was unknown in three cases. The interval was not statistically different between groups, with an average interval of 12.9 days in the patients with megakaryocytes and 15 days in the remaining cases (P = 0.644). Of the COVID-19-positive patients who had megakaryocytes identified in the cardiac microvasculature, 17 patients (17/23, 74%) were admitted to the ICU and none underwent ECMO. Nineteen patients (19/ 23, 82.61%) had COVID-19 pneumonia listed as the primary cause of death, with diffuse alveolar damage in three cases and superimposed bacterial pneumonia in one case. The causes of death in the remaining cases included malignancy (n = 2), multisystem organ failure (n = 2), and
Table 2. Premortem laboratory values

| Control Cases (Non-COVID) Premortem Laboratory Values |
|------------------------------------------------------|
| Case # | Platelet count: 150–400 K/μl, M: 150–450 K/μl | MPV 8.4–12.0 fl | CRP 0.0–3.0 mg/l | D-dimer <500 ng/ml xULNL | IL-6 < 1.8 pg/ml | Fibrinogen 200–450 mg/dl | PT 11.5–14.5 sec | PTT 23.8–36.6 sec | Troponin F: 0–9 ng/l, M: 0–14 ng/l |
|--------|-----------------------------------------------|----------------|----------------|-----------------------------|----------------|--------------------------|----------------|----------------|-------------------------------|
| 1      | –                                             | –              | –              | –                           | –              | –                        | –              | –                           | –                            |
| 2      | 190                                           | 9.9            | 8.3            | –                           | –              | 283                      | 17.2           | –                           | 13                            |
| 3      | 77                                            | 13.7           | –              | –                           | –              | 587                      | 14.3           | –                           | 19                            |
| 4      | –                                             | –              | –              | –                           | –              | –                        | –              | –                           | –                            |
| 5      | 103                                           | 11.8           | –              | –                           | –              | 449                      | 37.5           | 138.3                       | –                            |
| 6      | 390                                           | 11.5           | 53.6           | –                           | –              | –                        | 20             | –                           | –                            |
| 7      | –                                             | –              | –              | –                           | –              | –                        | –              | –                           | –                            |
| 8      | –                                             | –              | –              | –                           | –              | –                        | –              | –                           | –                            |
| 9      | 520                                           | 11.2           | 144.1          | >4000                       | 8              | 400                      | 32.5           | 57.2                        | 27                            |
| 10     | 348                                           | 11             | 23.5           | 1998                        | 4              | –                        | 13             | 29.8                        | 1911                          |
| 11     | 86                                            | 10.3           | >4000          | 8                           | –              | 602                      | 36.2           | 45.9                        | 2939                          |
| 12     | 290                                           | 10.9           | 71.3           | >4000                       | 8              | 69.6                     | 17.3           | –                           | 68                            |
| Overall average | 251                               | 11.3           | 60.2           | –                           | 8              | 464                      | 23.5           | 67.8                        | 830                           |
| Median | 251                                           | 11             | 57             | –                           | 8              | 457                      | 20             | 57                         | 68                            |
| Average (megakaryocytes present) | 255                               | 10.9           | 62.5           | –                           | –              | –                        | 24.5           | –                           | 1504                          |
| Median | 290                                           | 11             | 62             | –                           | 8              | 602                      | 20             | 46                         | 1504                          |
| Average (no megakaryocytes) | 248                               | 11.52          | 58.6           | –                           | 6              | 429.8                    | 22.9           | 75.1                        | 493                           |
| Median | 190                                           | 11             | 24             | –                           | 6              | 425                      | 17             | 57                         | 23                            |

| COVID-19+ Cases Premortem Laboratory Values |
|--------------------------------------------|
| Case # | Platelet count: 150–400 K/μl, M: 150–450 K/μl | MPV 8.4–12.0 fl | CRP 0.0–3.0 mg/l | D-dimer <500 ng/ml xULNL | IL-6 < 1.8 pg/ml | Fibrinogen 200–450 mg/dl | PT 11.5–14.5 sec | PTT 23.8–36.6 sec | Troponin F: 0–9 ng/l, M: 0–14 ng/l |
|--------|-----------------------------------------------|----------------|----------------|-----------------------------|----------------|--------------------------|----------------|----------------|-------------------------------|
| 13     | 116                                           | 11.9           | 78.2           | >4000                       | 8              | –                        | –60            | 33.3                       | >150                          |
| Case # | Platelet count F: 150–400 K/μl, M: 150–450 K/μl | MPV 8.4–12.0 fl | CRP 0.0–3.0 mg/l | D-dimer >500 ng/ml xULNL | IL-6 < 1.8 pg/ml | Fibrinogen 200–450 mg/dl | PT 11.5–14.5 sec | PTT 23.8–36.6 sec | Troponin F: 0–9 ng/l, M: 0–14 ng/l |
|-------|---------------------------------|-----------------|----------------|--------------------------|----------------|----------------------|----------------|----------------|-------------------|
| 14    | 120                             | 12.2            | 253            | >4000                    | 8              | 501                  | 64.4           | 44.1           | 243               |
| 15    | 268                             | 11              | 264            | 1374                     | 2.7            | –                    | –              | –              | 174               |
| 16    | 170                             | 12.2            | >300           | >4000                    | 8              | –                    | –              | –              | 88                |
| 17    | 114                             | 13.2            | MPV 8.4–12.0 fl| >5000                    | 10             | –                    | –              | –              | –                 |
| 18    | 161                             | 11.4            | 264            | 1374                     | 2.7            | –                    | 15.8           | 25.5           | 11                |
| 19    | 362                             | 11              | 70             | >4000                    | 8              | 234                  | 513            | 14.5           | 72.7              |
| 20    | –                               | –               | –              | –                        | –              | –                    | –              | –              | –                 |
| 21    | –                               | –               | –              | –                        | –              | –                    | –              | –              | –                 |
| 22    | 153                             | 12.6            | 104            | >4000                    | 8              | 395                  | 331            | 38.4           | –                 |
| 23    | 569                             | 9.2             | 144            | 1683                     | 3.4            | 8.1                  | 640            | 15.8           | –                 |
| 24    | 160                             | 10.6            | 45             | 2131                     | 4.3            | –                    | 593            | 19.8           | 32.9              |
| 25    | 264                             | 12.5            | 48             | >4000                    | 8              | 80                   | 493            | 23.3           | 37.2              |
| 26    | 642                             | 10.3            | –              | 725                      | 1.5            | 400                  | 480            | 13.8           | 29.2              |
| 27    | 348                             | 9.8             | 140            | 2176                     | 4.4            | 112                  | 672            | 15.5           | 35.1              |
| 28    | 146                             | 10.1            | 7.7            | 879                      | 1.8            | –                    | –              | 12.6           | –                 |
| 29    | 288                             | 9.7             | 6.1            | >5000                    | 10             | –                    | 664            | 13.5           | 29.8              |
| 30    | 331                             | 11.7            | 69             | >4000                    | 8              | –                    | 371            | 28.4           | 51.2              |
| 31    | 468                             | 9.6             | –              | 1084                     | 2.2            | 23.4                 | 727            | 13.7           | 39.2              |
| 32    | –                               | –               | –              | –                        | –              | –                    | –              | –              | –                 |
| 33    | 388                             | 11.7            | –              | 3362                     | 6.7            | 332                  | 15.9           | 51.1           | 50                |
| 34    | 309                             | 10.3            | –              | –                        | –              | –                    | –              | 14.2           | –                 |
| 35    | 309                             | 10.3            | 166            | >4000                    | 8              | 91.9                 | 758            | 13.4           | 33.1              |
| 36    | 137                             | 10.8            | 64             | –                        | 57.3           | –                    | 14.7           | 57.8           | 93                |

Table 2. (Continued)
| Case # | Platelet count F: 150–400 K/µl, M: 150–450 K/µl | MPV 8.4–12.0 fl | CRP 0.0–3.0 mg/l | D-dimer <500 ng/ml | IL-6 <1.8 pg/ml | Fibrinogen 200–450 mg/dl | PT 11.5–14.5 sec | PTT 23.8–36.6 sec | Troponin F: 0–9 ng/l, M: 0–14 ng/l |
|-------|-----------------------------------------------|------------------|-----------------|-----------------|----------------|-----------------|----------------|----------------|----------------|
| 37    | 10                                            | 9.9              | 279             | 2848            | 5.7            | 369             | 473            | 18             | 27.7           | 797            |
| 38    | –                                             | –                | –               | –               | –              | –               | –              | –              | –              | –              |
| 39    | –                                             | –                | –               | –               | –              | –               | –              | –              | –              | –              |
| 40    | 157                                           | 11.2             | 80              | >4000           | 8              | >400            | –              | –              | 66.4           | 29             |
| 41    | 47                                            | 11.6             | 44              | >4000           | 8              | 114             | 123            | 34.2           | 47.4           | 8              |
| 42    | 284                                           | 9.6              | –               | –               | –              | –               | –              | –              | –              | –              |
| 43    | 217                                           | 11.1             | 226.2           | >4000           | 8              | 32.5            | 483            | 13.7           | 67.3           | 73             |
| 44    | 86                                            | 10.3             | >300            | >4000           | 8              | 68.6            | 626            | 17.5           | 42.4           | 56             |
| 45    | 388                                           | 11.7             | –               | 3362            | 6.7            | 332             | –              | 15.9           | 51.1           | 50             |
| 46    | 65                                            | 12.6             | 96.1            | –               | –              | –               | –              | 18             | 44.3           | 296            |
| 47    | –                                             | –                | –               | –               | –              | –               | –              | –              | –              | –              |
| 48    | 37                                            | 9.7              | 53.3            | 1405            | 2.8            | –               | 531            | 29             | 13.5           | 9              |
| Overall average | 237    | 11     | 109           | 1914           | 6   | 153           | 514           | 21           | 45           | 115          |
| Median      | 194    | 11     | 79            | 1809           | 8   | 92            | 507           | 16           | 43           | 56           |
| Average (megakaryocytes present) | 284    | 11     | 104           | 1705           | 6   | 168           | 551           | 21           | 44           | 94           |
| Median      | 278    | 11     | 78            | 1683           | 8   | 102           | 553           | 16           | 37           | 55           |
| Average (no megakaryocytes) | 143    | 11     | 136           | 3105           | 7   | 122           | 466           | 18           | 49           | 166          |
| Median      | 112    | 11     | 80            | 2848           | 8   | 69            | 478           | 18           | 47           | 56           |
### Table 3. Significant autopsy findings

#### Control (Non-COVID) Cases Significant Autopsy Findings

| Case # | Megakaryocytes present | Megakaryocytes /cm 2 | Gross cardiac findings | Histologic cardiac findings | Pulmonary emboli |
|--------|-------------------------|-----------------------|------------------------|-----------------------------|------------------|
| 1      | No                      | –                     | –                      | Myocyte hypertrophy         | Yes              |
| 2      | No                      | –                     | –                      | Yes                         |                  |
| 3      | No                      | –                     | Cardiomegaly, CAD      | Focal replacement fibrosis, myocyte hypertrophy | No               |
| 4      | No                      | –                     | Cardiomegaly, left ventricular hypertrophy, left atrial dilation | Myocyte hypertrophy | Yes              |
| 5      | No                      | –                     | Cardiomegaly, biventricular hypertrophy and dilation, left atrial dilation, CAD s/p CABG, saphenous vein graft thrombosis | Acute myocardial infarction, multifocal remote myocardial infarcts | No               |
| 6      | Yes                     | 1.96                  | Cardiomegaly, four chamber hypertrophy, valvular heart disease | Myocyte hypertrophy | Yes              |
| 7      | Yes                     | 0.33                  | Cardiomegaly, CAD      | Acute myocardial infarction, multifocal remote myocardial infarcts | No               |
| 8      | Yes                     | 1.28                  | –                      | Multifocal acute to subacute thromboembolic microinfarctions | Yes              |
| 9      | No                      | –                     | CAD                    | Remote myocardial infarction, myocyte hypertrophy | No               |
| 10     | No                      | –                     | Cardiomegaly, CAD s/p CABG | Acute and remote myocardial infarction | No               |
| 11     | Yes                     | 0.30                  | –                      | Focal acute myocardial infarction | No               |
| 12     | Yes                     | 0.36                  | –                      | –                           | Yes              |

#### COVID+ Cases Significant Autopsy findings

| Case # | Megakaryocytes present | Megakaryocytes /cm 2 | Gross cardiac findings | Histologic cardiac findings | Pulmonary emboli |
|--------|-------------------------|-----------------------|------------------------|-----------------------------|------------------|
| 13     | Yes                     | 3.25                  | Cardiomegaly           | –                           | Yes              |
| 14     | Yes                     | 0.91                  | Cardiomegaly, CAD s/p CABG | Healing transmural myocardial infarction and microinfarcts, subendocardial myocyte vacuolization | No               |
| 15     | Yes                     | 0.48                  | Cardiomegaly, biventricular dilation, CAD | Healed subendocardial microinfarcts (focal) | No               |
| 16     | Yes                     | 2.86                  | Cardiomegaly, biventricular dilation, CAD | –                           | Yes (clinical)   |
| 17     | Yes                     | 0.77                  | Cardiomegaly, left ventricular hypertrophy, CAD | Remote myocardial infarction | Yes (clinical)   |
Table 3. (Continued)

COVID+ Cases Significant Autopsy findings

| Case # | Megakaryocytes present | # Megakaryocytes/cm² | Gross cardiac findings | Histologic cardiac findings | Pulmonary emboli |
|--------|-------------------------|----------------------|------------------------|----------------------------|-----------------|
| 18     | Yes                     | 4.58                 | CAD                    | Remote myocardial infarction, Acute subendocardial microinfarcts | Yes             |
| 19     | Yes                     | 3.75                 | –                      | –                           | Yes             |
| 20     | No                      | 0.64                 | Cardiomegaly, CAD      | Subendocardial myocyte vacuolization | No              |
| 21     | No                      | 2.72                 | Cardiomegaly, CAD s/p CABG | Healing transmural myocardial infarction and microinfarcts, subendocardial myocyte vacuolization | Yes             |
| 22     | No                      | 5.56                 | –                      | Myocarditis, myocyte hypertrophy | Yes             |
| 23     | No                      | 0.42                 | Cardiomegaly, left ventricular hypertrophy | Remote microinfarctions | No              |
| 24     | No                      | 0.63                 | Cardiomegaly           | –                           | Yes             |
| 25     | No                      | 0.42                 | Cardiomegaly, left ventricular hypertrophy, CAD | Remote myocardial infarction | No              |
| 26     | No                      | 0.40                 | Cardiomegaly           | –                           | No              |
| 27     | No                      | 1.81                 | CAD                    | Vascular congestion         | Yes             |
| 28     | No                      | 0.79                 | Cardiomegaly, biventricular hypertrophy and dilation, CAD | Acute and healing subendocardial infarction | Yes             |
| 29     | No                      | 0.69                 | Left ventricular hypertrophy, CAD | –                         | Yes             |
| 30     | No                      | 3.85                 | CAD                    | Focal acute microinfarcts, myocyte hypertrophy | No              |
| 31     | No                      | 0.79                 | Cardiomegaly, biventricular dilation, left ventricular hypertrophy | Focal acute ischemic changes | No              |
| 32     | No                      | 1.23                 | –                      | –                           | Yes             |
| 33     | No                      | 2.78                 | Cardiomegaly, CAD s/p CABG | –                         | No              |
| 34     | No                      | 1.00                 | –                      | –                           | No              |
| 35     | No                      | 0.40                 | Cardiomegaly, biventricular dilation and hypertrophy, biatrial enlargement | Focal acute ischemic changes | Yes             |
| 36     | No                      | –                    | Cardiomegaly, biventricular hypertrophy and left atrial enlargement | Acute myocardial infarction | Yes             |
| 37     | No                      | –                    | CAD with acute plaque change | Replacement fibrosis | No              |
| Case # | # Megakaryocytes present | Megakaryocytes /cm² | Gross cardiac findings | Histologic cardiac findings | Pulmonary emboli |
|--------|--------------------------|----------------------|------------------------|----------------------------|-----------------|
| 38     | No                       | –                    | Biventricular hypertrophy | –                          | No              |
| 39     | No                       | –                    | Right ventricular dilation | –                          | Yes             |
| 40     | No                       | –                    | Atrial enlargement, patent foramen ovale, CAD | –                          | No              |
| 41     | No                       | –                    | Cardiomegaly | Remote myocardial infarction and microinfarcts | Yes             |
| 42     | No                       | –                    | CAD | Acute subendocardial microinfarcts, remote myocardial infarction | Yes             |
| 43     | No                       | –                    | CAD s/p CABG | Amyloidosis, remote myocardial infarction | Yes             |
| 44     | No                       | –                    | Dilated cardiomyopathy, CAD | –                          | No              |
| 45     | No                       | –                    | Benign myxoma, CAD | –                          | No              |
| 46     | No                       | –                    | Cardiomegaly, biventricular dilation | –                          | No              |
| 47     | No                       | –                    | N/A | N/A | No |
| 48     | No                       | –                    | – | N/A | No |
atherosclerosis. Pulmonary emboli were reported in 13 (13/23, 56%), compared with five (5/19, 38%) of cases without megakaryocytes.

Megakaryocytes were identified in five (5/12, 40%) of prepandemic autopsies (Figure 1B). An average of 2.6 megakaryocytes were detected per section, or 0.84 megakaryocytes per cm². The average age of prepandemic cases with megakaryocytes was 70.6 years, compared with 66.6 in the remaining cases. All five patients were admitted to the ICU, and causes of death included bronchopneumonia (n = 2, with atherosclerotic coronary artery disease contributing in one case), diffuse alveolar damage (n = 2, with usual interstitial pneumonia contributing in one case), and multisystem organ failure due to thromboembolism in one case. Pulmonary emboli were reported in three cases (3/5, 60%), compared with three (3/7, 43%) cases without megakaryocytes.

COVID-19 autopsies with detected megakaryocytes, average laboratory values were as follows: platelet count = 284.3 K/µl (range, 120–642), MPV = 11.07 fl (range, 9.2–13.2), CRP = 103.8 mg/l (range, 6.3 – >300), fibrinogen = 551.0 mg/dl (range, < 60–748), IL-6 = 168.1 pg/ml (range, 8.1–400), PT = 21.14 sec (range, 12.6–64.4), PTT = 43.50 sec (range, 25.5 – >150). D-dimer levels, expressed as multiples of upper limit of normal, averaged 5.99 (range, 1.5–10). In prepandemic autopsies with detected megakaryocytes, average laboratory values were as follows: platelet count = 255.3 K/µl (range, 86–390), MPV = 10.90 fl (range, 10.3–11.5), CRP = 62.45 mg/l (range, 53.6–71.3), PT = 24.50 sec (range, 17.3–36.2). PTT was only documented in one case, resulting at 45.9 sec. D-dimer levels, expressed as multiples of upper limit of normal, averaged 8.00 (range, 4–8). Fibrinogen and IL-6 were only documented once, resulting at 602 mg/dl and 69.6 pg/ml, respectively.

We compared laboratory values in cases with and without cardiac megakaryocytes, and between COVID-19 and prepandemic autopsies with detectable megakaryocytes (Table 4). Platelet counts were significantly higher in COVID-19-positive cases, with
megakaryocytes present compared to those without megakaryocytes, with an average of 284 K/µl in cases with megakaryocytes present, and 143 K/µl in cases without (P = 0.0157; difference between means and SEM = −141.5 ± 55.03). All other platelet parameters showed no statistically significant differences between groups (Figure 2). In COVID-19 autopsies, the average number of megakaryocytes per section and per cm² was 5.78 (range, 1–22) or 1.77 per cm² (range, 0.40–3.85). In prepandemic autopsies, an average of 2.6 megakaryocytes were identified per section (range, 1–5) or 0.84 per cm² (range, 0.30–1.96). However, there was no statistically significant difference in megakaryocyte quantification between COVID-19-positive and prepandemic autopsies with detectable megakaryocytes. There was no relationship between antiplatelet therapy and number of cardiac megakaryocytes (P = 0.4234).

Discussion

Postmortem examinations remain a powerful tool to understand pathologic manifestations of disease. Undoubtedly, they have been invaluable in our understanding of COVID-19. Although there has been much interest in the effects of COVID-19 on cardiac tissue, there are limited reports of cardiac megakaryocytes in the literature. We report the presence of megakaryocytes within the microvasculature of 23 (23/36, 64%) of COVID-19 autopsies in our institution, and in five prepandemic cases without COVID-19 (5/12, 40% of selected cases). This finding is frequent, but not ubiquitous in COVID-19 autopsies. The presence of megakaryocytes in the heart of non-COVID patients suggests this may be a nonspecific inflammatory response, rather than a response to viral infection. Given the focus on platelets and thrombosis in COVID-19 manifestations, it is important to consider that the presence of megakaryocytes in the heart is not exclusive to COVID-19 pathology and that this finding should not be overinterpreted as a finding characteristic of SARS-CoV-2 infection.

The finding of megakaryocytes within the cardiac microvasculature is not a novel finding, although there are few contemporary studies describing this phenomenon. As part of investigative efforts to determine the origin of megakaryocytes, Brill and Halpern examined multiple organs in a series of autopsies which represented neoplastic, infectious, inflammatory, and cardiovascular etiologies.46 In 45 cases with available cardiac tissue, megakaryocytes were detected in 13% of cases. The largest study to date, published by Smith and Butcher in 1952, reviewed 180 total autopsy cases and compared the incidence of megakaryocytes in the heart and other tissues between in-hospital deaths and “sudden deaths” such as accidental injuries.47 By assessment of routine histologic sections, the authors reported the presence of megakaryocytes in the heart, lung, liver, spleen, kidney, adrenal and pituitary glands, brain, lymph nodes, pancreas as well as the marrow. Cardiac megakaryocytes were described in 16% of “sudden death” cases, compared with 45% of hospital deaths.

The morphology of cardiac megakaryocytes differs from that of their marrow-based counterparts, rendering them difficult to detect on routine histologic sections (Figure 1). Megakaryocytes in peripheral capillaries are smaller in size, with less cytoplasm, and frequently have hypolobated, round nuclei that may be distorted by the shape of vascular channels. Therefore, it can be challenging to distinguish true megakaryocytes from degenerating cardiac myocyte nuclei. The unique morphology of cardiac megakaryocytes, and sparse distribution among the tissue, suggests that this finding may be underreported in routine assessment. The megakaryocyte-specific immunohistochemical detection method provides a useful means for accurate identification.

Due to our study size, it is difficult to correlate the presence of cardiac megakaryocytes and thrombotic events. Among the COVID-19 autopsy patients,
| Case # | Cause of Death                                                                 | # Megakaryocytes/cm² | Gross cardiac findings | Histologic cardiac findings | Pulmonary emboli | MPV K/µl | CRP mg/l | D-dimer ng/ml xULN | IL-6 pg/ml | Fibrinogen mg/dl | PT sec | PTT sec | Prothrombin F: % |
|--------|-------------------------------------------------------------------------------|----------------------|------------------------|----------------------------|-----------------|----------|----------|---------------------|------------|------------------|---------|----------|------------------|
| 6      | Usual interstitial pneumonia with diffuse alveolar damage                      | 1.96                 |                        | Cardiomegaly-yes, four chamber hypertrophy, valvular heart disease | Yes             | 390      | 11.5     | 53.6                | –          | –                | –       | –       | –                |
| 7      | Bronchopneumonia in the setting of coronary artery disease                     | 0.33                 |                        | Cardiomegaly, CAD          | Acute myocardial-infarction, multifocal remote myocardial infarcts | No       | –        | –                   | –          | –                | –       | –       | –                |
| 8      | Multisystem organ failure due to thromboembolism                              | 1.28                 |                        |                            | Multifocal acute to subacute thromboembolic microinfarctions | Yes      | –        | –                   | –          | –                | –       | –       | –                |
| 11     | Diffuse alveolar damage                                                       | 0.30                 |                        | Focal acute myocardial-infarction | No              | 86       | 10.3     | >4000                | 8          | –                | 602     | 36.2   | 45.9             |
| 12     | Bronchopneumonia                                                              | 0.36                 |                        |                            |                  | 290      | 10.9     | >4000                | 8          | 69.6             | –       | 17.3   | 68               |

**COVID-19 Positive Autopsies**

| Case # | Cause of Death                                                                 | # Megakaryocytes/cm² | Gross cardiac findings | Histologic cardiac findings | Pulmonary emboli | MPV K/µl | CRP mg/l | D-dimer ng/ml xULN | IL-6 pg/ml | Fibrinogen mg/dl | PT sec | PTT sec | Prothrombin F: % |
|--------|-------------------------------------------------------------------------------|----------------------|------------------------|----------------------------|-----------------|----------|----------|---------------------|------------|------------------|---------|----------|------------------|
| 13     | COVID-19 pneumonia with DAD                                                  | 3.25                 |                        | Cardiomegaly-yes           |                  | 116      | 11.9     | >4000                | 8          | –                | –       | 33.3   | >150             |
| 14     | COVID-19 pneumonia s/p CABG                                                  | 0.91                 |                        | Cardiomegaly-yes, CAD      | Healing transmural-myocardial-infarction and microinfarcts, subendocardial myocyte vacuolization | No        | 120      | 12.2     | >4000                | 8          | –                | 501     | 64.4   | 44.1             |

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Table 4. (Continued)

| Case # | Cause of Death | Megakaryocytes/cm² | Gross cardiac findings | Histologic cardiac findings | Pulmonary emboli | CRP | D-dimer | IL-6 | Fibrinogen | PT | PTT | Troponin F |
|--------|----------------|---------------------|------------------------|-----------------------------|------------------|-----|---------|------|-------------|----|-----|-----------|
| 15     | COVID-19 pneumonia with DAD | 0.48 | Cardiomegaly, biventricular dilatation, CAD | Healed subendocardial microinfarcts (focal) | No | 268 | 11 | 155 | 1935 | 2.8 | – | – | – | 57 |
| 16     | COVID-19 infection with superimposed bacterial pneumonia | 2.86 | Cardiomegaly, left ventricular hypertrophy, CAD | – | Yes (clinical) | 170 | 12.2 | >300 | >4000 | 8 | – | 639 | 14.3 | 84.4 | 88 |
| 17     | COVID-19 pneumonia | 0.77 | Cardiomegaly, left ventricular hypertrophy, CAD | Remote myocardial infarction | Yes (clinical) | 114 | 13.2 | 6.3 | >5000 | 10 | – | – | – | 174 |
| 18     | COVID-19 pneumonia | 4.58 | CAD | Remote myocardial infarction, Acute subendocardial microinfarcts | Yes | 161 | 11.4 | 264 | 1374 | 2.7 | – | – | 15.8 | 25.5 | 11 |
| 19     | COVID-19 pneumonia | 3.75 | – | – | Yes | 362 | 11 | 70 | >4000 | 8 | 234 | 513 | 14.5 | 72.7 | 7 |
| 20     | COVID-19 pneumonia | 0.64 | Cardiomegaly, CAD | Subendocardial myocyte vacuolized-ion | No | – | – | – | – | – | – | – | – |
| 21     | COVID-19 pneumonia | 2.72 | Cardiomegaly, CAD s/p CABG | Healing transmural myocardial infarction and microinfarcts, subendocardial myocyte vacuolized-ion | Yes | – | – | – | – | – | – | – | – |
| 22     | COVID-19 pneumonia with DAD | 5.56 | – | Myocarditis, myocyte hypertrophy | Yes | 153 | 12.6 | 104 | >4000 | 8 | 395 | 331 | 3.8 | X | 40 |
| Case # | Cause of Death                      | # Megakaryocytes/cm² | Gross cardiac findings | Histologic cardiac findings | Pulmonary emboli | Platelet count | CRP 0.0-3.0 | D-dimer <500 ng/ml | IL-6 ≤ 1.8 xULNL | Fibrinogen 200-450 mg/dl | PT 11.5-14.5 sec | PTT 23.8-36.6 sec | Teqponin F: 0-9 ng/l, M: 0-14 ng/l |
|--------|-------------------------------------|----------------------|------------------------|-----------------------------|------------------|----------------|-------------|-------------------|----------------------|-----------------------------|------------------|----------------------|---------------------|
| 23     | COVID-19 pneumonia                  | 0.42                 | Cardiomegaly, left ventricular hypertrophy | Remote myocardial infarction | No               | 569            | 9.2         | 144               | 168            | 3.4                      | 8.1               | 640                  | 15.8                | X                  | 122                 |
| 24     | COVID-19 pneumonia                  | 0.63                 | Cardiomegaly           | Yes                          |                  | 160            | 10.6        | 45                | 2131              | 4.3                      | –                | 593                  | 19.8                | 32.9               | 66                  |
| 25     | COVID-19 pneumonia                  | 0.42                 | Cardiomegaly, left ventricular hypertrophy, CAD | Remote myocardial infarction | No               | 264            | 12.5        | 48                | >4000              | 8                        | 80               | 493                  | 23.3                | 37.2               | 52                  |
| 26     | COVID-19 pneumonia                  | 0.40                 | Cardiomegaly-y         | No                           |                  | 642            | 10.3        | –                | 725               | 1.5                      | 400              | 480                  | 13.8                | 29.2               | –                   |
| 27     | COVID-19 pneumonia                  | 1.81                 | CAD                    | Vascular congestion          | Yes              | 348            | 9.8         | 140               | 2176              | 4.4                      | 112              | 672                  | 15.5                | 35.1               | 295                 |
| 28     | Aortic atherosclerosis with intestinal necrosis in setting of Acute MI | 0.79                 | Cardiomegaly, biventricular hypertrophy and dilation, CAD | Acute and healing subendocardial infarction | Yes              | 146            | 10.1        | 7.7               | 879               | 1.8                      | –               | –                    | 12.6                | –                  | –                   |
| 29     | COVID-19 pneumonia                  | 0.69                 | Left ventricular hypertrophy, CAD | –                            | Yes              | 288            | 9.7         | 6.1               | >5000              | 10                        | –               | 664                  | 13.5                | 29.8               | 20                  |
| 30     | Gastrointestinal stromal tumor      | 3.85                 | CAD                    | Focal acute myocardial infarcts, myocyte hypertrophy | No               | 331            | 11.7        | 69                | >4000              | 8                        | –               | 371                  | 28.4                | 51.2               | 26                  |
| 31     | COVID-19 pneumonia                  | 0.79                 | Cardiomegaly, biventricular dilation, left ventricular hypertrophy | Focal acute ischemic changes | No               | 468            | 9.6         | –                | 1084              | 2.2                      | 23.4             | 727                  | 13.7                | 39.2               | 38                  |
| 32     | COVID-19 pneumonia                  | 1.23                 | –                      | Yes                          |                  | –              | –           | –                | –                   | –                        | –               | –                    | –                   | –                  | –                   |
platelet counts were indeed significantly higher in cases with megakaryocytes present compared to those without megakaryocytes, with an average platelet count of 284.3 K/μl in cases with megakaryocytes present and 142.8 K/μl in cases without megakaryocytes ($P = 0.0157$; difference between means and SEM = $-141.5 \pm 55.03$). However, it is unclear what contribution cardiac megakaryocytes make, if any, to overall platelet production. Cardiac megakaryocytes in this group may be reflective of increased megakaryopoiesis in the marrow and therefore thrombopoiesis, rather than a causal relation. Previously published postmortem evaluation of bone marrow in COVID-19 autopsies showed increased megakaryocytes in 15% of examined cases.\textsuperscript{48} It has been postulated that elevations in IL-6 in severe COVID-19 may stimulate megakaryopoiesis and platelet production in marrow and pulmonary megakaryocytes.\textsuperscript{49} There were no significant differences in clotting parameters (PT, PTT); a greater proportion of cases with megakaryocytes in the heart had pulmonary emboli either diagnosed clinically or detected at autopsy. In cases with megakaryocytes present, 13 COVID-19 cases (13/23, 56%) and three control cases (3/5, 60%) had pulmonary emboli present, compared with five (5/16, 38%) of the remaining COVID-19 cases and three (3/7, 47%) of the remaining control cases ($P = 0.3618$).

The role of platelets in disease has been more widely studied than that of their precursor cell. Platelets receive their mRNA repertoire from megakaryocytes via highly regulating pathways during thrombopoiesis.\textsuperscript{50,51} Despite lacking a nucleus, platelets have active spliceosome machinery and can process mRNA, which may play a role in platelet activation.\textsuperscript{52} Evidence of alterations in the platelet transcriptome and proteome have been described in diverse diseases, such as myocardial infarction, sepsis, malignancy, autoimmune disease such as lupus, and aging.\textsuperscript{53} In the absence of disease, platelet gene expression has been demonstrated to be stable in individuals over time.\textsuperscript{54} \textit{In vitro} studies have demonstrated similar transcriptional and translational studies in response to sepsis in mice comparable to those in patient-derived platelets and demonstrate higher amounts of zⅡβ directly correlating with survival.\textsuperscript{55} High levels of procoagulant platelets have been implicated in noninfectious inflammatory conditions as well, such as arterial thrombotic disease.\textsuperscript{56} Platelets are known to contribute to the development of atherosclerosis through induction of SOCS3 in plate cells, with resultant inflammatory cytokine production (IL6, IL1β, and TNF-α) and impaired phagocytic capacity, thus contributing to sustained plaque formation.\textsuperscript{19}
There is some evidence that megakaryocytes may also play a role in the development or response to a noninfectious inflammatory condition, as increased numbers of circulating megakaryocytes have been detected in patients following acute myocardial infarction. As megakaryocytes have a longer lifespan than the 9–11 day circulation period of their progeny, much is left to be discovered regarding their potential role in development of and response to disease states, as well as how these transcriptomic and proteomic changes are conveyed to platelets.

The role of platelets and megakaryocytes in SARS-CoV-2 infection is under active investigation and of interest, as characterization of the immune response to SARS-CoV-2 may aid in stratification of patients and improve management. Whether the altered platelet function observed in COVID-19 is a result of viral interactions or systemic inflammation is unclear, both processes have potential to contribute to the observed platelet phenotype in severe COVID-19. Both platelets and megakaryocytes are thought to be active in innate immunity, and antiviral activity has been previously demonstrated during viral infections. Internalization of influenza by platelets has been previously described through a phagocytosis-like process with subsequent digestion.

SARS-CoV-2 virions has been identified in circulating platelets, and studies of platelet RNA expression demonstrate alterations in pathways associated with Mitogen-activated protein kinase activation, ubiquitination, antigen presentation, mitochondrial dysfunction, and upregulation of antiviral proteins such as Interferon-induced transmembrane protein 3 (IFTM3). Interestingly, uptake of SARS-CoV-2 results in increased expression of pathways responsible for programmed cell death, suggestive of a probable role in viral clearance. Taken together, these findings suggest platelets are active, not passive, factors in the acute response to infection by SARS-CoV-2.

The potential role of megakaryocytes in the response to infection by SARS-CoV-2 is not well understood. In response to influenza and dengue virus, megakaryocytes overexpress IFTM3 and may play a regulatory role in response to infection. There is conflicting evidence regarding the ability of SARS-CoV-2 to directly enter megakaryocytes. Retrospective analysis of published deep-sequencing and microarray data have not demonstrated Angiotensin-converting enzyme 2 (ACE2) expression on megakaryocytes. Although megakaryocytes are not known to express the ACE2 receptor, recent studies have demonstrated expression of ACE2 in platelet in vitro. Transcriptomic studies have shown expression of CD147 on primary megakaryocytes and proposed this receptor as a means of entry. Barrett et al. recently reported visualization of SARS-CoV-2 virions in megakaryocytes within the bone marrow and replicating SARS-CoV-2 detected in the pulmonary megakaryocyte from a deceased COVID-19 patient; however, this finding has not been identified by other authors.

Much of our understanding of megakaryocyte function is based on study of the bone marrow; however, there is a growing body of evidence to suggest functional and phenotypic differences in other tissue locations, namely, a more robust immunoinflammatory function. The lung is the best described of these extramedullary sites. Flow cytometric and transcriptomic studies in murine models show a greater proportion of lung megakaryocytes express markers of terminal maturation, suggestive of priming for efficient platelet production. Interestingly, lung megakaryocytes express greater levels of immune molecules compared to those residing in the marrow, with inducible immunophenotypic changes reminiscent of antigen-presenting cells. Lung megakaryocytes show elevated expression of markers including MHC II, CD80, CD40, ICAM-1, LFA-1, and CCR7 compared to their marrow counterparts. Further studies are needed to elucidate a specific role for megakaryocytes and platelets in COVID-19, and more generally in immunoregulatory roles, and how this role differs in the setting of tissues outside of the bone marrow.

Limitations of our study include sample size and patient selection, as patients who undergo autopsy at our institution may not be representative of the overall population. Moreover, control cases were retrospectively selected from institutional records by the authors. Documentation is limited in some cases, and laboratory and prescription data were not universally available for reporting.

In summary, the presence of megakaryocytes in the heart is not unique to COVID-19, as these/our findings demonstrate the presence of megakaryocytes in the hearts of patients that died from noninfectious causes and other viral infections. Our findings suggest the presence of megakaryocytes in the cardiac microvasculature may be a nonspecific response to systemic inflammatory stimuli or pulmonary dysfunction, rather than a specific or coordinated response to infection. Notably, the presence of increased pulmonary and cardiac megakaryocytes has not been correlated with overall platelet production, nor has their abundance at autopsy been related to clinical thrombosis. The pathologic role of megakaryocytes found in cases of patients who died from SARS-CoV-2 infection is unclear. Randomized controlled trials of the use of aspirin or P2Y12 inhibitors have found no
benefit when used with heparin anticoagulation in both moderately ill and critically ill patients to date (RECOVERY, ACTIV-4-A, REMAP-CAP), suggesting that these megakaryocytes and the platelets they produce may play little role in the development of the thromboinflammation and microvascular thrombosis that characterizes severe COVID-19.

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Author contributions

EM Battinelli, O Pozdnyakova, R Padera, J Connors, and KL Gawelek designed the research study. G Pinkus implemented the immunohistochemical procedures. R Padera conducted autopsies of the COVID-19 cohort. KL Gawelek selected prepandemic cases, and gathered clinical and laboratory data for all cases. KL Gawelek, R Padera, and O Pozdnyakova reviewed the histology and immunostains. KL Gawelek and EM Battinelli performed statistical analysis. KL Gawelek wrote the article and constructed figures with discussion and feedback from all authors. EM Battinelli, O Pozdnyakova, R Padera, J Connors, and KL Gawelek edited the article.

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Conflict of interest

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this article.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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