International Journal of Surgical Pathology
1–11

DOI: 10.1177/10668969221102534
journals.sagepub.com/home/ijs
SAGE

Placental Pathology After SARS-CoV-2 Infection in the Pre-Variant of Concern, Alpha / Gamma, Delta, or Omicron Eras

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Abstract

Objectives. The goal of this study is to describe placental pathology after infection with SARS-CoV-2 before the predominance of variants of concern (pre-VOC) and during eras of predominant transmission of the Alpha & Gamma (co-circulating), Delta, and Omicron variants. *Methods.* We used county-level variant data to establish population-level variant proportions, SARS-CoV-2 PCR to identify cases, and IgG serology to exclude latent infections from controls and histopathologic examination to identify placental pathology. *Results.* We report findings in 870 placentas from pregnancies complicated by SARS-CoV-2 including 90 with infection in the Alpha/Gamma era, 60 from the Delta era and 56 from the Omicron era. Features of maternal vascular malperfusion (MVM), including decidual arteriopathy, were significantly more frequent after SARS-CoV-2 infection. The risk of these findings varied over time, with the highest rates in the Delta era. Increased COVID-19 severity and the presence of comorbidities strengthened these associations. *Conclusion.* MVM is a feature of SARS-CoV-2 infection in pregnancy. Lesion frequency changed with the predominant circulating virus and should be considered with new variants.

Keywords

placenta, SARS-CoV-2, variants of concern, maternal vascular malperfusion, decidual arteriopathy, COVID-19

Introduction

Pregnant patients with SARS-CoV-2 infection have a higher risk of hospitalization, severe disease, and death compared to similarly-aged non-pregnant women with SARS-CoV-2.[1] SARS-CoV-2 infection is also associated with adverse pregnancy outcomes, including a possible increased risk of preterm birth and, rarely, vertical transmission or stillbirth.[2–8] In utero exposures to infection may have life-long consequences. Rates of adverse outcomes, including stillbirth, have increased with variants of concern (variants), including the Delta variant.[8]

The placenta is the physiologic interface between maternal and fetal circulation and is responsible for providing a fetus with resources needed for growth and development. As such, it is also in many ways the "black box "of pregnancy – maternal and fetal conditions that impact growth and maturation often leave marks on the placenta which can be diagnosed on pathologic examination after birth. For example, maternal hypertensive disorders, including preeclampsia, are associated with the pathologic finding of maternal vascular malperfusion (MVM) in the placenta.

Pathologic examination of placentas from women with SARS-CoV-2 infection during pregnancy may provide insight into the intrauterine stresses experienced by their fetuses. The first studies of placentas from women infected with SARS-CoV-2 suggested an increased incidence of fetal vascular malperfusion (FVM), sequelae of perturbations of fetal circulation through the placenta, or decidual arteriopathy, damage to maternal decidual vessels.[9,10] Subsequent studies have varied from case reports or

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small case series to larger studies of around 100 placentas.[11] While some studies re-demonstrated FVM[12] or MVM,[11] others have not demonstrated any significant placental findings in women with SARS-CoV-2 infection.[13] A meta-analysis conducted in the summer of 2021 reported findings suggestive of placental hypoperfusion and inflammation in pregnancies complicated by SARS-CoV-2 infection,[14] while a more recent meta-analysis suggested that there are no typical placental findings.[15] However, the majority of these studies have looked at broad categories of placental pathology, ie MVM or FVM, rather than at a more granular level, eg components of MVM such as decidual arteriopathy or accelerated villous maturation independently, and most of these studies do not include control groups of placentas without SARS-CoV-2 infection. Additionally, published studies generally do not relate diagnosis frequency to strain or timing within the pandemic. Heterogeneity across viral strains, when analyzed collectively as opposed to sequentially, may mask clinically relevant findings.

We have now collected placentas from SARS-CoV-2 positive pregnant women for nearly two years, including during the waves of the Alpha/Gamma, Delta, and Omicron variants. Given the heterogeneity in prior results that may be informed by sample selection and variant prevalence, our objective was to provide a large, comprehensive, and well controlled study of the impact of SARS-CoV-2 infection in pregnancy on the placenta and to examine the impact of COVID-19 disease severity and presence of comorbidities.

Methods

Patients were included if they delivered between March 18, 2020 and February 14, 2022. Prior to April 30, 2021, we collected specimens on all patients with SARS-CoV-2 delivering at our institution, an academic medical center in a large urban area. Afterward, we transitioned to purposeful recruitment of patients with first or second trimester infection, moderate to critical COVID-19, or infection during a period with high prevalence of variants. Routine testing for SARS-CoV-2 was performed for all admissions to Labor & Delivery during the entire study period.

Placental examination was performed using the Amsterdam Criteria.[16] Individual features of MVM and FVM are reported, as is the frequency of identifying any MFM feature or any FVM features. Accelerated and delayed villous maturation were diagnosed clinically on the basis of villous maturation different from that expected by gestational age in the areas of villous diameter, abundance of syncytial knots, stromal cellularity, stromal density, and position of capillaries. For statistical purposes, we grouped cases where the diagnosis was qualified as "mild", "patchy", "regional" or otherwise into the parent diagnosis. Decidual arteriopathy is a parent category diagnosed when mural hypertrophy of membrane arterioles, persistent muscularization of basal plate arterioles (which we consider equivalent to incomplete remodeling of spiral arterioles), atherosis or fibrinoid necrosis are present. Formal diagnoses of MVM or FVM are reported separately. Individual practice varies, but members of our section generally render a formal diagnosis when multiple features of MVM or FVM are present; for example, MVM is diagnosed when accelerated villous maturation, decidual arteriopathy, and infarct are all present. Less often, a formal diagnosis is made or suggested when a single feature is extremely prominent, such as a macroscopic focus of avascular villi for FVM.

Histologic slides were imaged on a Leica GT450 scanner at 40× objective magnification.

Clinical information was abstracted from the electronic health record and stored in a REDCap database.[17] Comorbidity data were abstracted from the electronic health record using the following ICD9/10 codes. Obesity: 278, E66, O99.21*; Diabetes: 250, 648.0*, E08, E10, E11, O24; Hypertension: 642, 401, I10, O10-15; where * includes any sub-codes. Pre-pregnancy body mass index was not available for most patients; therefore we were reliant on formal diagnosis of obesity.

The trimester of SARS-CoV-2 infection was determined using the gestational age of diagnosis of COVID-19. COVID-19 disease severity was determined using CDC criteria.[18]

Controls were patients without history of vaccination, no history of SARS-CoV-2 infection in pregnancy, and negative SARS-CoV-2 PCRs during routine admission testing. To rule out prior asymptomatic infection we tested for anti-SARS-CoV-2 spike protein IgG and IgM levels similar to that previously described.[19] Positive immunity, defined as signal/cutoff > 1.0 AU/ml, was identified in 21 of 206 patients tested (10.3%). Those patients were excluded as infection could have been during or prior to the current pregnancy, complicating interpretation of their biospecimen.

To characterize proportions of SARS-CoV-2 clades circulating in our patient catchment area, lineage data was downloaded from the GISAID public sequence database for all isolates collected between Jan 1, 2021 and April 1, 2022 and identified as having been isolated from either [our city] or [our county]. Isolates were identified as Alpha if they belonged to pango lineage B.1.1.7 or any Q sublineages (ie Q.1, etc), Gamma if they belonged to lineage P.1 or any sublineages (ie P.1.1, etc), Delta if they belonged to lineage B.1.647.2 or any sublineages (ie AY.1, etc) and Omicron if they belonged to lineage B.1.1.529 or any sublineages (ie BA.1, etc). Of note, our institution is the major contributor to GISAID for our geographic locale, so these data should represent our patient population. The Pre-VOC, Alpha/Gamma, Delta, and Omicron eras were delineated based on the most frequent

variant and shifted to the nearest week. Era boundaries were set by an investigator that was unaware of the placental diagnoses. Of note, some SARS-CoV-2 diagnoses in our population were self-reported without a specific date, therefore not all cases can be definitively assigned to an era. They are excluded from era-specific analyses.

For descriptive values, quantitative values are reported as mean +/- standard deviation. Categorical variables are reported as counts and percentages. Bivariable analyses utilized Student's t-test for continuous variables or Fisher exact test comparing SARS-CoV-2 or subgroups against the controls only. We used Benjamini and Hochberg's method to control for multiple comparisons, with corrected P-value based on the number of placental lesions tested for each population with a false discovery rate of 0.05. The study was approved by the institutional review board as STU00212232. Multivariable analyses were performed controlling for birthing person characteristics that significantly differed in bivariable analyses ($p < 0.05$).

Results

Defining Population Level Variant of Concern Eras

The Alpha and Gamma variants of SARS-CoV-2 were first identified in our population in the second week of February 2021. These variants rose together in frequency through the week of June 6, 2021 (Figure 1). Delta first appeared the week of April 25 but became dominant in the week of June 27, 2021. Omicron became predominant in the week of December 19, 2021. Based on these estimates, we categorized patients based on the date of their first positive swab as: Pre-VOC: 3/2020–2/2021, Alpha/Gamma: 3/2021–6/2021, Delta: 7/2021–12/18/2021, Omicron: 12/19/2021 – present.

Patient Demographics and Infection Details

There were 185 controls and 883 patients with SARS-CoV-2 infection. Of those with SARS-CoV-2 infection, 673 were in the pre-variant of concern era, 90 in the Alpha/Gamma era, 60 in the Delta era, and 56 in the Omicron era. Characteristics of the sample are depicted in Table 1. Patients with SARS-CoV-2 infection were, on average, slightly younger than controls and less likely to be multiparous. The utilization of public insurance differed strikingly between populations:more individuals with SARS-CoV-2 infection utilized public insurance compared to controls. Comorbidity rates were broadly similar, however patients in the Omicron era were more likely to be diagnosed as obese. Individuals with SARS-CoV-2 delivered at earlier gestational ages and were more likely to deliver preterm compared to controls. The incidence of cesarean section was similar between groups. SARS-CoV-2 disease severity was similar between different eras, though Omicron cases were more likely to be symptomatic. Omicron era patients had a preponderance of third trimester infection, possibly reflecting study timing.

SARS-CoV-2 Infection is Associated with Maternal Vascular Malperfusion and Decidual Arteriopathy

We tested the association of SARS-CoV-2 infection with different placental lesions and categories of lesions. The strongest association was with the presence of any feature of maternal vascular malperfusion (MVM), which was identified in 87 of 185 controls (47%), as compared to 555 of 883 patients with SARS-CoV-2 infection (63%, OR 1.9, $p < .001$, Figure 2, Table 2, Supplementary Table 1). MVM describes a constellation of findings associated with hypertensive disorders of pregnancy, fetal growth restriction, preterm delivery, and stillbirth. Among the major findings in MVM, decidual arteriopathy (DA) was identified in 23 of 185 controls (12%) as compared to 227 of 883 patients with SARS-CoV-2 (26%, OR 2.4, $p < .001$). Decidual arteriopathy includes a group of lesions associated with failure of uterine blood vessels to adapt to pregnancy and resulting injury to those vessels. Among the decidual arteriopathies, the signal is driven by incomplete remodeling of basal plate arterioles (OR 3.8, $p < .001$). We previously reported an association between infection and atherosis with fibrinoid necrosis, a particularly severe lesion, however the association is not statistically significant in this cohort ($p = 0.23$). Other features of MVM, such as accelerated villous maturation were also elevated, as was a formal "topline" diagnosis of MVM (Table 2, Supplementary Table 1).

Results from multivariable analyses using logistic regression and controlling for gestational age, insurance type, gravidity, and parity were similar to the bivariable analyses (Supplementary Table 1).

Associations with Variants of Concern

SARS-CoV-2 infection in the Alpha / Gamma and Delta eras was associated with MVM features (Figure 2, Table 2, Supplementary Table 1). MVM feature were seen in 87 of 185 controls (47%), as opposed to 59/90 patients in the Alpha / Gamma era (65%, $p < .001$). Infection in the Delta era had an even higher risk with MVM features seen in 49/56 (82%, $p < .001$), though Omicron showed a weaker signal, with MVM features in only 31/40 (55%, p = ns). Delta (18/56, 30%, OR 3.0, $p < 0.01$) and Omicron (18/40, 32%, OR 3.9, $p < 0.01$) era infections were associated with decidual arteriopathy. Delta era infection was associated with accelerated villous maturation, seen in 10/60 (17%, OR 3.5, $p < 0.05$). Finally, Delta and Omicron era infections were associated with a formal diagnoses of MVM (10% and 11%, OR 6.7 and 7.3, $p < 0.01$ and <0.01, respectively). Associations of Delta and Omicron era infection with decidual arteriopathy and formal diagnosis of MVM and between Delta era infection and MVM features and accelerated

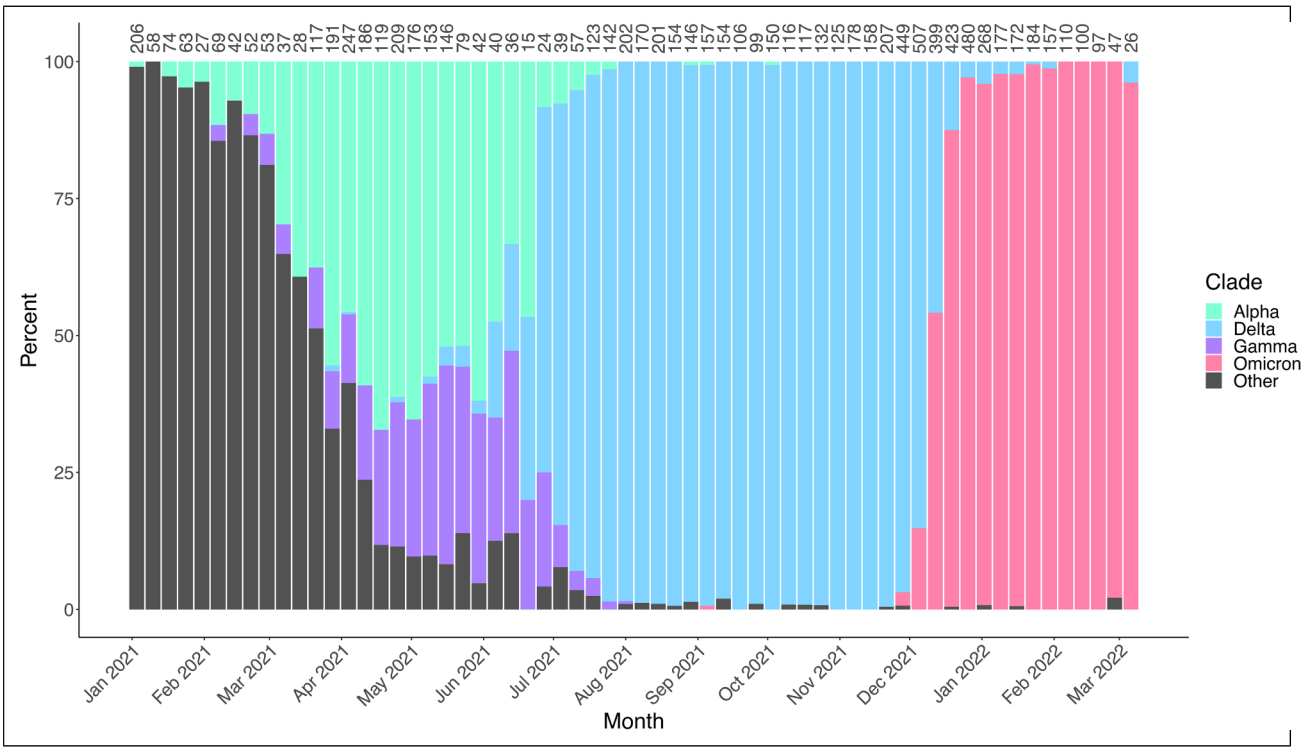

Figure 1. SARS-CoV-2 variant frequency over time. Alpha and Gamma variants emerge together and become dominant March 2021 – June 2021. Delta appears in April but represents almost all infections by the week of June 27, 2021. Omicron becomes dominant December 19, 2021. Numbers above the graph indicate the number of patients sampled that week.

maturation survived correction for multiple comparison testing (Supplementary Table 2). Placental weights were slightly lower in the Delta era.

FVM and features of FVM have frequently been reported in association with SARS-CoV-2. Among FVM features, delayed villous maturation was observed in 38 controls (21%), as compared to 129 SARS-CoV-2 cases (15%, p = ns) and 109 pre-VOC cases (18%, p = ns). Delayed villous maturation was less frequent in the Delta era with 5 cases (8.3%, OR = 0.35, $p < 0.05$) and the Omicron era with 4 cases (7.1%, OR 0.29, $p < 0.05$). Other FVM features did not significantly differ with infection (Table 2). A formal diagnosis of FVM was made in 12 controls (6.5%) as opposed to 52 SARS-CoV-2 cases (5.9%, p = ns), 33 pre-VOC cases (4.9%, p = ns), 6 Alpha / Gamma era cases (6.7%, p = ns), 6 Delta cases (10%, p = ns) and 6 Omicron cases (11%, p = ns). Any feature of FVM was identified in 80 controls (43%), 455 SARS-CoV-2 cases (52%), 346 pre-VOC cases (51%), 43 Alpha / Gamma era cases (48%), 32 Delta cases (53%), and 31 Omicron cases (55%).

Association with Severity

We tested the association of COVID-19 severity with placental lesions (Figure 3, Supplementary Table 1). Any MVM feature was present in 87/185 controls (47%) as compared to 142/245 patients with asymptomatic SARS-CoV-2 (58%, OR 1.6, $p < 0.05$), 290/449 of those with mild COVID-19 (65%, OR 2.1, $p < 0.001$) and 60/92 of those with moderate to severe disease (65%, $p < 0.01$). A similar trend was seen for decidual arteriopathy, with decidual arteriopathy in 23/185 controls (12%), as compared with 72/245 with asymptomatic SARS-CoV-2 (29%, OR 2.9, $p < 0.001$), 100/449 with mild COVID-19 (22%, OR 2.0, $p < 0.01$), and 33/92 with moderate to severe COVID-19 (36%, OR 3.9, $p < 0.001$). Similar trends were seen for the component decidual arteriopathies and formal diagnosis of MVM. Interestingly, accelerated villous maturation was sharply and significantly elevated in moderate to severe COVID-19, seen in 26/92 cases (28%) as compared to 10/185 in controls (5.4%, OR 6.9, $p < 0.001$)

Association with Comorbidities

We tested the association of SARS-CoV-2 infection in the presence or absence of comorbidities, defined here as any diagnosis of hypertension in pregnancy, diabetes in pregnancy, or diagnosed obesity (Figure 4). Overall, MVM features were more pronounced with either comorbidities or SARS-CoV-2, and were most pronounced when both were present, however the relatively small number of control patients with comorbidities (34) hampered

Table 1. Patient Characteristics.

	Controls (n = 185)	SARS-CoV-2 (n = 883)	Pre-VOC (n = 673)	Alpha/ Gamma (n = 90)	Delta (n = 60)	Omicron (n = 56)
Maternal age (years)	32.8 + /-4.9	31.3 + /-5.6	31.6 + /-5.7	30.9 + /-5.7	29.8 + /-5.6	29.7 + /-5.1
Gravida	2.1 + /-1.4	2.5 + /-1.6	2.5 + /-16	2.5 + /-1.7	2.5 + /-1.6	2.4 + /-1.5
Para	1.6 + /-0.9	1.4 + /-1.2	1.3 + /-1.1	1.4 + /-1.5	1.1 + /-1.2	0.7 + /-1.2
Multiparous	178 (96)	635 (72)	511 (76)	58 (64)	38 (63)	26(46%)
Public insurance (n = 185, 881, 672, 90, 60, 55)	29 (16)	367 (42)	263 (39)	37 (41)	33 (55)	32(58)
Hypertension in pregnancy	20(11)	131(15)	106(16)	14(16)	8(13)	3(5.4)
Diabetes in pregnancy	12(6.5)	69(7.8)	65(9.4)	2(2.2)	2(3.3)	2(3.6)
Obesity diagnosis	5(2.7)	**59(6.7)**	43(6.4)	6(6.7)	3(5)	**7(12.5)**
Any comorbidity	34(18)	210(24)	170(25)	19(21)	11(18)	10(18)
SARS-CoV-2 disease severity:	N/A					
Asymptomatic		245 (28)	176 (26)	28 (31)	11 (18)	30(54)
Mild		449 (51)	359 (54)	40 (44)	31 (52)	18(32)
Moderate		62 (7)	53 (7.9)	4 (4.4)	4 (6.7)	1(1.8)
Severe		30 (3.4)	17 (2.5)	6 (6.7)	5 (8.3)	2(3.6)
Unknown		97 (11)	68 (10)	12 (13)	9 (15)	5(8.9)
Trimester of first positive test:	N/A					
first		96 (11)	82 (12)	9 (10)	1 (1.7)	0 (0)
second		202 (23)	170 (25)	22 (24)	8 (13)	2 (3.6)
third		585 (66)	421 (63)	59 (66)	51 (85)	54 (96)
Gestational age at delivery (wks)	38.9 + /-1.6	**38.4 + /-2.6**	**38.5 + /-2.5**	38.8 + /-1.9	**37.6 + /-3.3**	**37.9 + /-3.7**
Method of delivery:						
Vaginal	133 (72)	639 (72)	475 (71)	68 (76)	48 (80)	46(82)
Cesarean	52 (28)	244 (28)	198 (29)	22 (24)	12 (20)	10(18)
Placental weight (g, intact singletons, n = 177, 870, 660, 90, 56)	465 + /-94	461 + /-112	465 + /-111	446 + /-117	**425 + /-119**	447 + /-90

comparisons. Specifically, any feature of MVM was seen in 69/151 non-comorbid controls and 18/34 comorbid controls (46% vs. 53%, p = ns), as compared to 414/673 patients with SARS-CoV-2 without comorbidities (62%, OR 1.9, p < 0.01 vs. non-comorbid controls) and 141/210 (67%, OR 2.4, p < 0.001 vs. non-comorbid controls). Accelerated villous maturation was seen in 6/151 non-comorbid controls (4.0%) as opposed to 4/34 comorbid controls (12%, p = ns), 64/673 non-comorbid SARS-CoV-2 patients (9.5%, OR 2.5, p < 0.04 vs. non-comorbid controls) and 42/210 comorbid SARS-CoV-2 patients (20%, OR 6.0 p < 0.001 vs. non-comorbid controls and OR 2.4, p < 0.001 vs. non-comorbid SARS-CoV-2 patients). Decidual arteriopathy was seen in 15/151 non-comorbid controls (10%) versus 8/34 comorbid controls (24%, OR 2.8, p = 0.04), 156/673 non-comorbid SARS-CoV-2 patients (23%, OR 2.7, p < 0.001 vs. non-comorbid controls) and 71/210 comorbid controls (34%, OR 4.6, p < 0.001 vs. non-comorbid controls and OR 1.7 p < 0.01 vs. non-comorbid SARS-CoV-2). Delayed villous maturation was seen in 34 of 151 non-comorbid controls versus 4/34 comorbid controls (22% vs. 11%, p = ns), 111 of 673 non-comorbid SARS-CoV-2 patients (16.4%, p = ns) and 18/210 comorbid SARS-CoV-2 patients (8.6%, OR 0.47, p < 0.01).

Changing Lesion Frequency Over the Course of the Pandemic

We determined the frequency of each lesion among patients diagnosed with SARS-CoV-2 in a particular month between March 2020 and February 2022 (Figures 5 and 6 Supplementary Table 2). MVM features waned slightly toward the end of the pre-VOC era, before increasing with Alpha / Gamma and markedly increasing with Delta. Decidual arteriopathy was very frequent in April 2020 but became steadily less common in patients with SARS-CoV-2 over time, before increasing again in the Delta and Omicron eras.

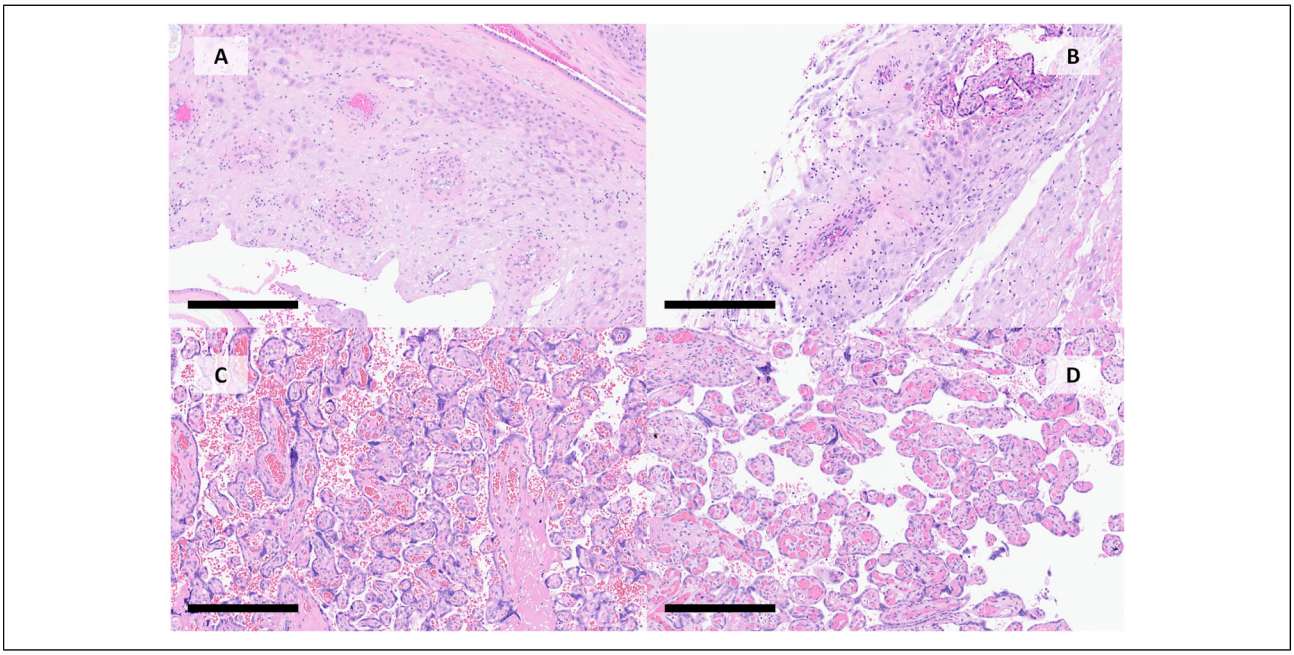

Figure 2. Histology. Representative H&E images of placental diagnoses. Mural hypertrophy of membrane arterioles (A). Persistent muscularization of basal plate arterioles (B). Accelerated villous maturation at 37 weeks gestation, characterized by lower villous diameter, increased stromal density and syncytial knots (C). versus Delayed villous maturation at 39 weeks gestation characterized by larger villous diameter, looser stroma, increased vascularity, and fewer syncytial knots (D). Objective magnification 10x, scale bar 300 µm.

Table 2. Lesions Associated with SARS-CoV-2 and Variant Infection.

	Controls (n = 185)	SARS-CoV-2 (n = 883)	Pre-VOC (n = 673)	Alpha / Gamma (n = 90)	Delta (n = 56)	Omicron (n = 40)
MVM						
Accelerated villous maturation	10(5.4)	106(12)**	80(12)**	11(12)	10(17)*	4(7.1)
Decidual arteriopathy	23(12)	227(26)***	175(26)***	14(16)	18(30)**	18(32)**
Atherosis and fibrinoid necrosis	1(0.5)	19(2)	14(2)	1(0.5)	2(3.4)	2(5)
Mural hypertrophy of membrane arterioles	17(9)	168(17)**	114(17)**	9(10)	10(17)	17(27)**
Persistent muscularization of basal plate arterioles	5(2.7)	84(9.5)**	71(11)***	8(9)*	3(5)	2(3.6)
Formal diagnosis of MVM	3(1.6)	55(6)*	37(5.5)*	5(5.6)	6(10)**	6(11)**
Any MVM feature	87(47)	555(63)***	413(61)***	59(65)**	49(82)***	31(55)
FVM						
Clustered avascular villi	33(18)	155(18)	127(19)	11(12)	11(18)	5(8.9)
Villous stromal vascular karyorrhexis	12(6.5)	77(8.7)	57(8.5)	10(11)	4(6.7)	5(8.9)
Fetal vascular thrombosis or intramural fibrin deposition	21(11)	128(14)	88(13)	13(14)	13(22)	14(25)*
Stem villous obliteration	14(7.6)	40(7.6)	34(5)	2(2.2)	2(3.3)	2(3.5)
Delayed villous maturation	38(21)	129(15)	109(16)	10(11)	5(8.3)*	4(7.1)*
Abnormal umbilical cord (hypercoiled etc)	23(12)	168(19)*	124(18)	14(16)	11(18)	18(32)*
Formal diagnosis of FVM	12(6.5)	52(5.9)	33(4.9)	6(6.7)	6(10)	6(11)
Any FVM feature	80(43)	455(52)	346(51)	43(48)	32(53)	31(55)

Values are frequency(%). FVM: Fetal vascular malperfusion; MVM: Maternal vascular malperfusion. *: uncorrected $p < 0.05$, **: $p < 0.01$; ***: $p < 0.001$.

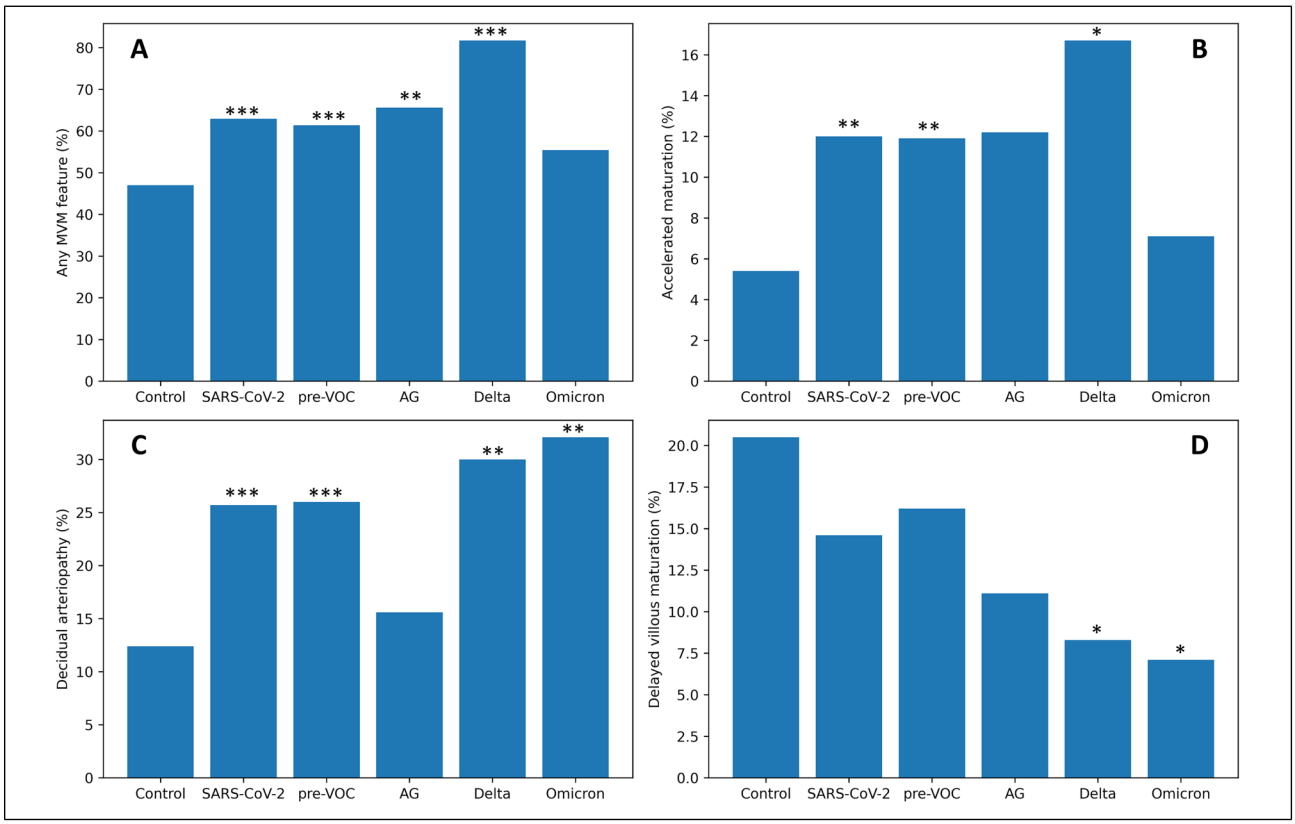

Figure 3. SARS-CoV-2 infection is associated with increased risk of MVM findings, particularly decidual arteriopathy. SARS-CoV-2 infection, or variant of concern other than Omicron, was associated with the presence of at least 1 MVM feature (A). Accelerated villous maturation was increased in SARS-CoV-2 and delta. (B). Decidual arteriopathy was associated with SARS-CoV-2 infection in the pre-VOC era, but the association weakened in the Alpha / Gamma era. It was stronger in the Delta and Omicron (C). Delayed villous maturation was decreased (D). after SARS-CoV-2 infection, significantly so in the Delta and Omicron eras. ***: uncorrected $p < 0.001$, **: $p < 0.01$, *:$p < 0.05$. MVM: maternal vascular malperfusion; pre-VOC: era prior to any predominant variant of concern.

Discussion

SARS-CoV-2 infection in pregnancy is strongly associated with features of maternal vascular malperfusion, specifically decidual arteriopathy. This association is more pronounced in eras of high-circulation of Alpha/Gamma,, Delta, and Omicron variants. MVM and decidual arteriopathy frequency were also increased with more severe COVID-19.

While the present study includes 50-fold more patients with SARS-CoV-2 than the earliest studies, it upholds similar conclusions.[10] Decidual arteriopathy was reported in 7 of 15 patients (47%), representative of the point estimates seen in our study in April 2020 (see Figure 3). Over the course of the pandemic, the frequency of decidual arteriopathy has decreased. Our current findings do not support an association of atherosis and fibrinoid necrosis with SARS-CoV-2 infection.

The same effect of random sampling which caused us early studies to over-estimate the association between SARS-CoV-2 infection and placenta pathologic findings may have impacted other small studies which failed to identify an association of SARS-CoV-2 with MVM features or DA. Some larger studies may have low baseline rates of MVM features or DA, making it more difficult for them to detect changes.[20] Interobserver variability may also drive some disagreement, as agreement for MVM features is low.[21] Studies using pandemic-era controls have not generally performed SARS-CoV-2 serology to exclude possible silent infection in pregnancy. Our findings (see **Methods**) suggest 10% of such controls could be latent cases, decreasing study power.

MVM represents a constellation of findings that are associated with hypertensive disorders in pregnancy, including preeclampsia. Decidual arteriopathy represents a collection of lesions involving failed adaptation of uterine vessels during pregnancy and is considered causative of preeclampsia. The interaction of SARS-CoV-2 infection, COVID-19 severity, and comorbidities, including hypertension in pregnancy, diabetes in pregnancy, and pre-pregnancy obesity is complex. More severe COVID-19 in pregnancy has been associated with comorbidities.[22,23] Conversely, SARS-CoV-2 infection in pregnancy has been reliably associated with the subsequent development of pre-eclampsia.[24(p)] Our data are agnostic as to

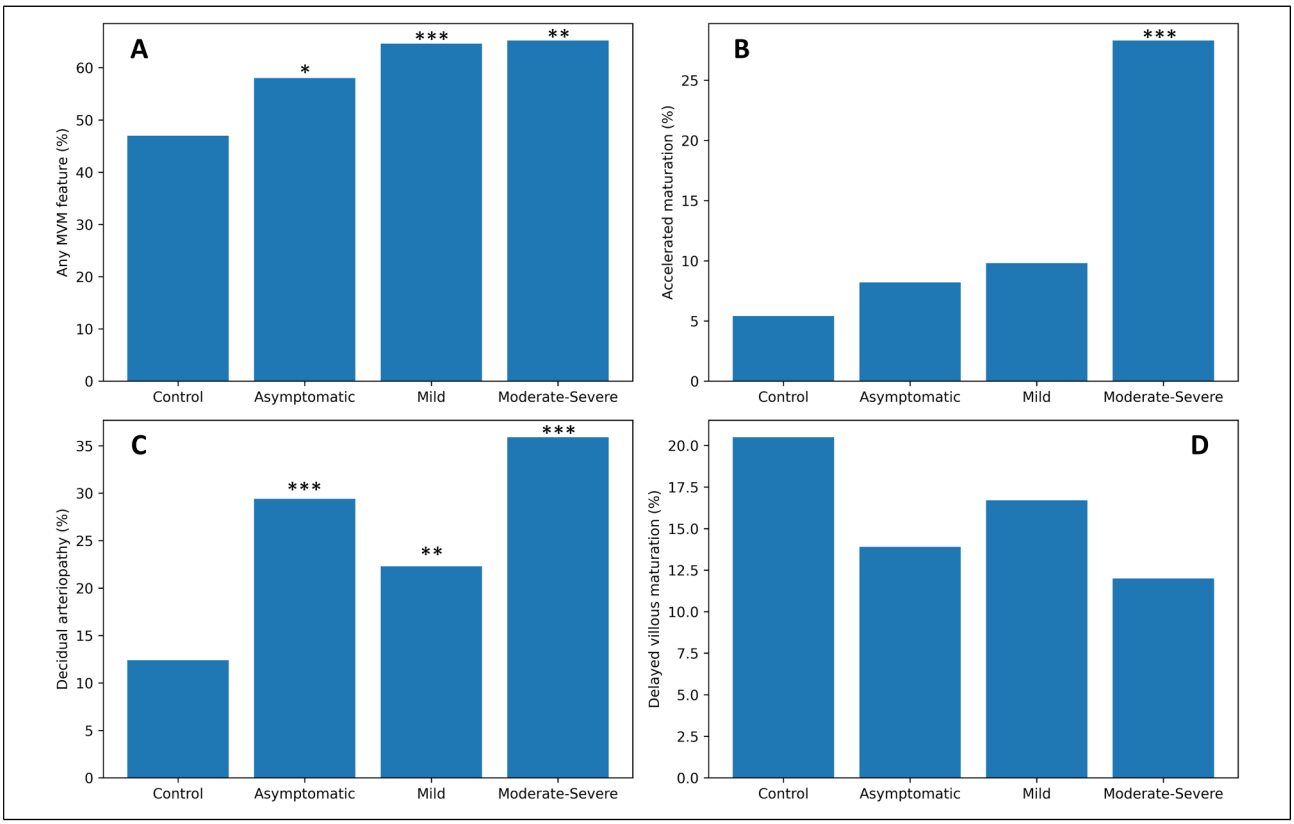

Figure 4. Increasing severity of COVID-19 is associated with increased risk of MVM findings. Asymptomatic SARS-CoV-2 infection was associated with the presence of at least 1 MVM feature, with increasing risk in mild or moderate to severe COVID-19 (A). Accelerated villous maturation was markedly increased after moderate to severe COVID-19 (B). Decidual arteriopathy was associated with SARS-CoV-2 infection at all severities, but particularly moderate to severe disease (C). Delayed villous maturation was non-significantly decreased in all severities of COVID 1-9 (D). ***: uncorrected $p < 0.001$, **: $p < 0.01$, *:$p < 0.05$. MVM: maternal vascular malperfusion.

causation, but support that 1) in patients without co-morbidities, SARS-CoV-2 infection is associated with the presence of MVM features including decidual arteriopathy and accelerated villous maturation and 2) among patients with SARS-CoV-2 infection, the presence of comorbidities is associated with increased rates of decidual arteriopathy and accelerated villous maturation.

The changes in lesion frequency over time indicate that placental pathology in response to SARS-CoV-2 is not fixed, but varies by the demographics of the pandemic, treatment, and viral strain. SARS-CoV-2 strains also show regional differences in prevalence over time. Our contemporaneous data allow us to impute the probable viral strain of a larger dataset, suggesting another possible explanation for the discordance between our findings and other, geographically disparate studies.

Limitations

This study is subject to several limitations. It is a single center study. Pathology data are largely from clinical examination, where pathologists were generally aware of the patient's SARS-CoV-2 infection status. SARS-CoV-2 variants were imputed based on population prevalence, rather than testing of the actual patient specimens. This is likely to manifest as imperfect boundaries – for example, patients with infection in July 2021 are extreme outliers in terms of MVM prevalence, possibly representing a mélange of different variants.

Conclusion

Examination of placental pathology from patients with SARS-CoV-2 infection in pregnancy showed elevated risk of MVM and DA, particularly with infection in the eras of the Delta or Omicron variants.

Acknowledgements

This study was supported by a grant from the Friends of Prentice (to JAG) and from the Stanley Manne Children's Research Fund Springboard Award (to LBM). JAG is

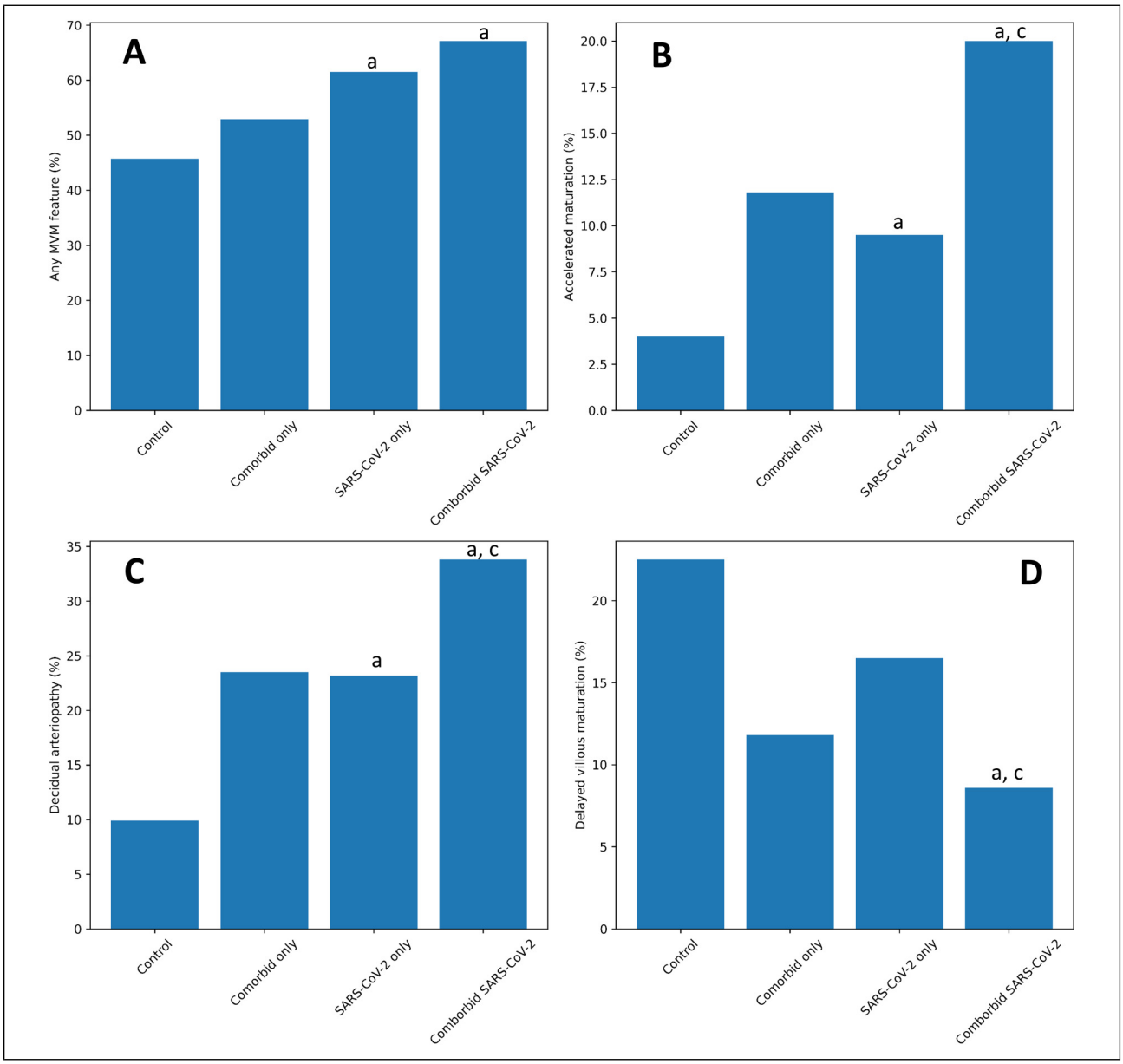

Figure 5. Impact of comorbidities on MVM in the context of SARS-CoV-2 infection. In a stepwise fashion comorbidities, SARS-CoV-2, and SARS-CoV-2 with comorbidities are associated with increased risk of any feature of MVM (A). particularly, accelerated villous maturation (B) and decidual arteriopathy (C). The risk of abnormally delayed villous maturation is decreased (D). Groups are compared using chi-squared and post-hoc Fisher exact tests. a: significantly different from non-comorbid controls; c: significantly different from non-comorbid SARS-CoV-2. MVM: maternal vascular malperfusion.

supported by the National Institute of Biomedical Imaging and Bioengineering K08EB030120. LBM is supported by the National Institute of Allergy and Infectious Diseases K23AI139337.

The authors wish to thank the staff of the Northwestern Prentice Women's Hospital Obstetric COVID Unit, the Northwestern Memorial Hospital Blood Bank, Chemistry Lab, and Pathology Gross Room, for going above and beyond for over a year to continue to make this study possible. Additional clinical data collection was performed by Ashwin Sunderraj, Allison Sakowicz, and Allaa Fadl-Alla.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Institute of Allergy and Infectious Diseases, Stanley Manne Children's Research Fund

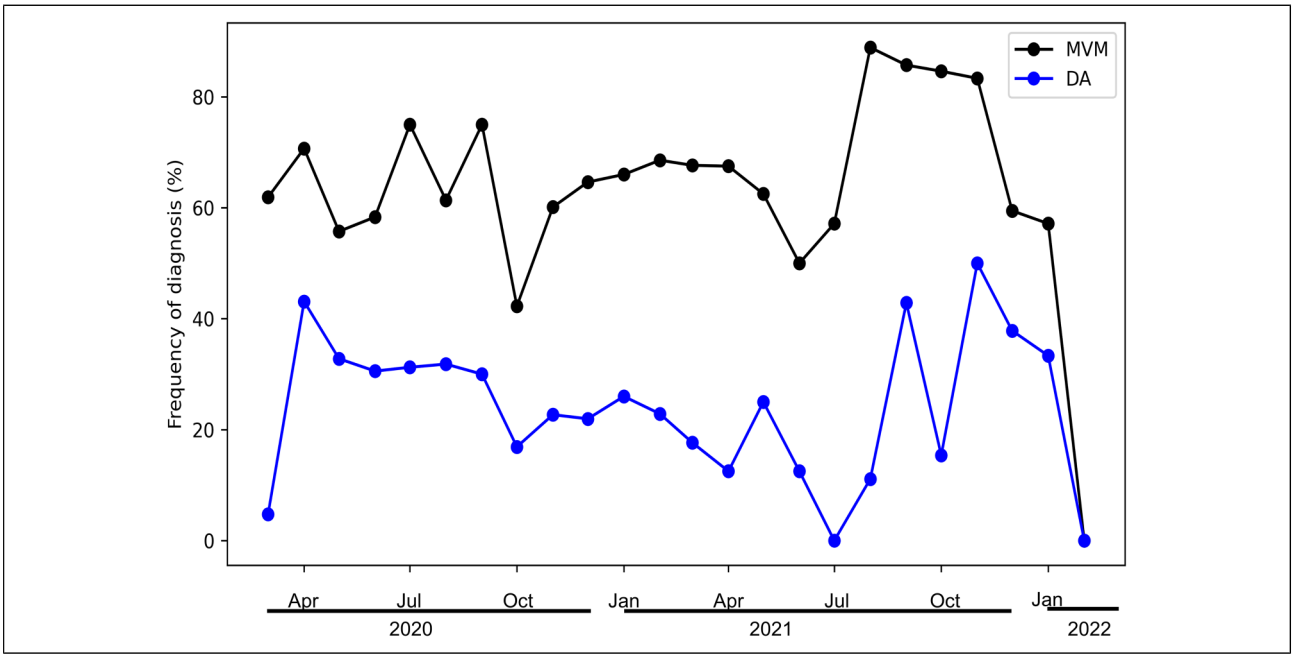

Figure 6. Frequency of selected diagnoses throughout the pandemic. Features of MVM (black line) were identified in 60% of patients with symptomatic SARS-CoV-2 diagnosed in April 2020, but only 29% of patients diagnosed with SARS-CoV-2 in October 2020. Decidual arteriopathy (blue line) rates mirrored those of MVM overall. Note there are only 2 patients in February 2022.

Springboard Award, Friends of Prentice, National Institute of Biomedical Imaging and Bioengineering, (grant number K23AI139337, 2020, K08EB030120).

Ethical Approval

The study was approved by the Northwestern University institutional review board as STU00212232.

Informed Consent

Informed consent was waved by the institutional review board.

Trial Registration

Not a clinical trial

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Supplemental material

Supplemental material for this article is available online.

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