COVID-19 Related Thrombotic Complications Before and During Delta Wave.

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No disclosures

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Contents

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Epidemiology

CDC data tracker 2021:

- Cumulative cases reported in the US: 79,555,000 (24,271 per 100,000)
- Total deaths reported in the US: 967,881 (until 3/21/2022).

  75.2% are 65 year and over

  18.2% are 50-65 years old

  6.6% are 49 years and under
- During the summer of 2021 peak (06/2021-09/2021), more than 2,000 hospital admissions with confirmed COVID-19 in Miami-Dade County.

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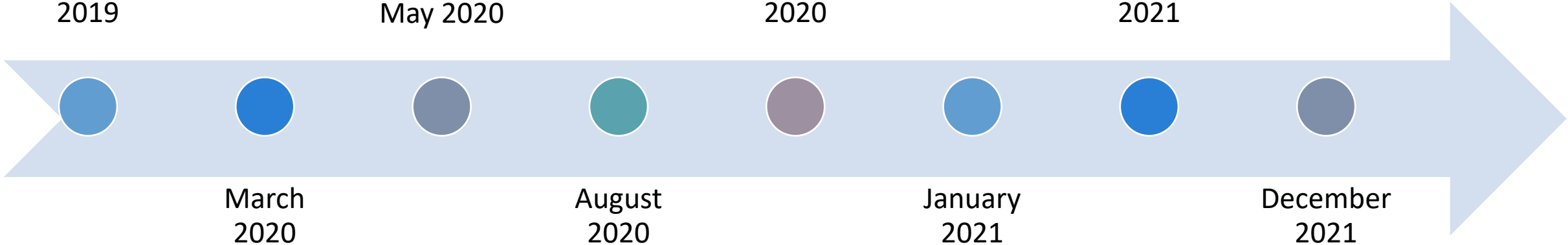
Pandemic timeline



December 2019

COVID-19 was reported

March 2020

- Pandemic declared
- Scarce information
- More admissions

May 2020

Vascular complications identified in patient with severe COVID-19

August 2020

- Authorization of convalescent plasma
- Use of Dexamethasone
- Ivermectin*
- Hydroxychloroquine*

November 2020

- Vaccination was proven effective
- Remdesivir
- Lopinavir/ritonavir*

January 2021

VOC concept emerged

August 2021

- Delta variant peak
- IL-6 receptor blockers

December 2021

Monoclonal antibodies (Sotrovimab, Casirivimab-imdevimab)

1. WHO Therapeutics Steering Committee. Therapeutics and COVID-19. Living Guideline. WHO/2019-nCoV/therapeutics/2021.1 ed. World Health Organization 31 March 2021.
2. Carvalho, T., Krammer, F. & Iwasaki, A. The first 12 months of COVID-19: a timeline of immunological insights. *Nat Rev Immunol* **21,** 245–256 (2021). https://doi.org/10.1038/s41577-021-00522-1

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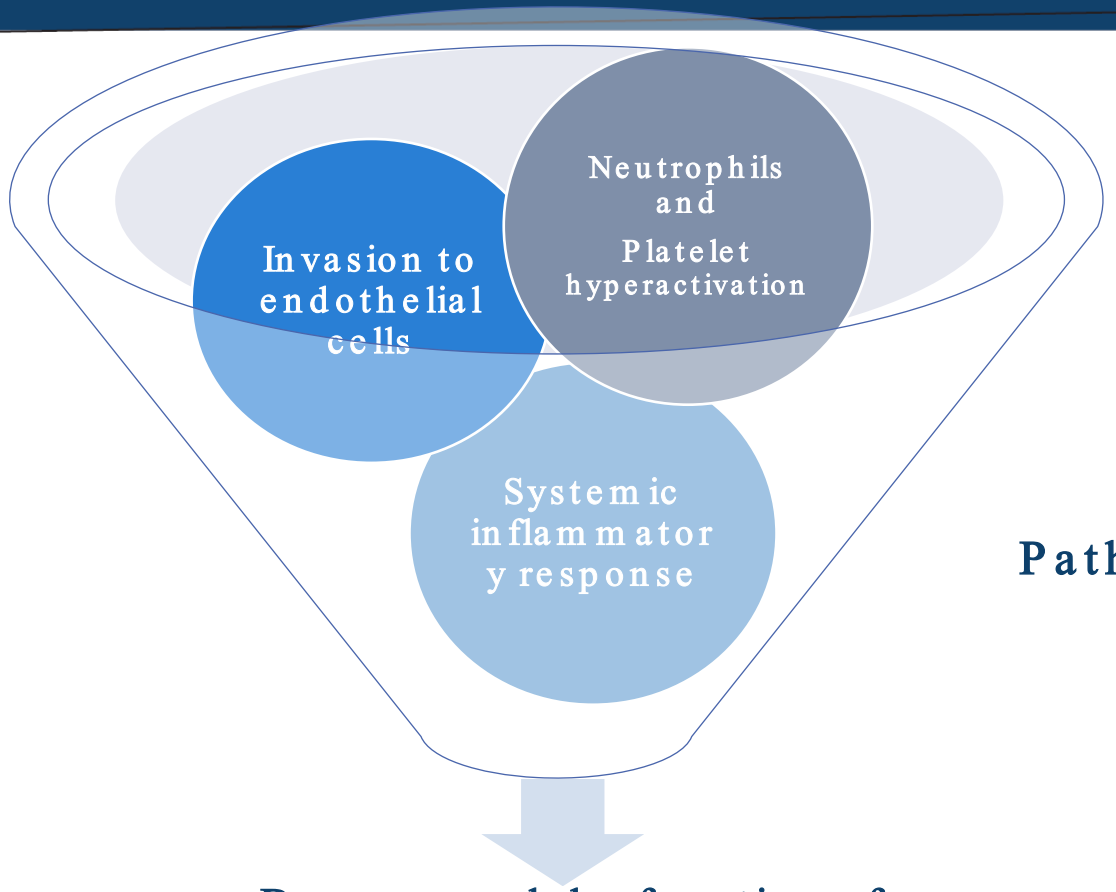
COVID and thrombosis



Pathophysiologic mechanisms

Damage and dysfunction of endothelium

Hypercoagulability

Teuwen, L. A., Geldhof, V., Pasut, A., & Carmeliet, P. (2020). COVID-19: the vasculature unleashed. Nature reviews. Immunology, 20(7), 389–391. https://doi.org/10.1038/s41577-020-0343-0

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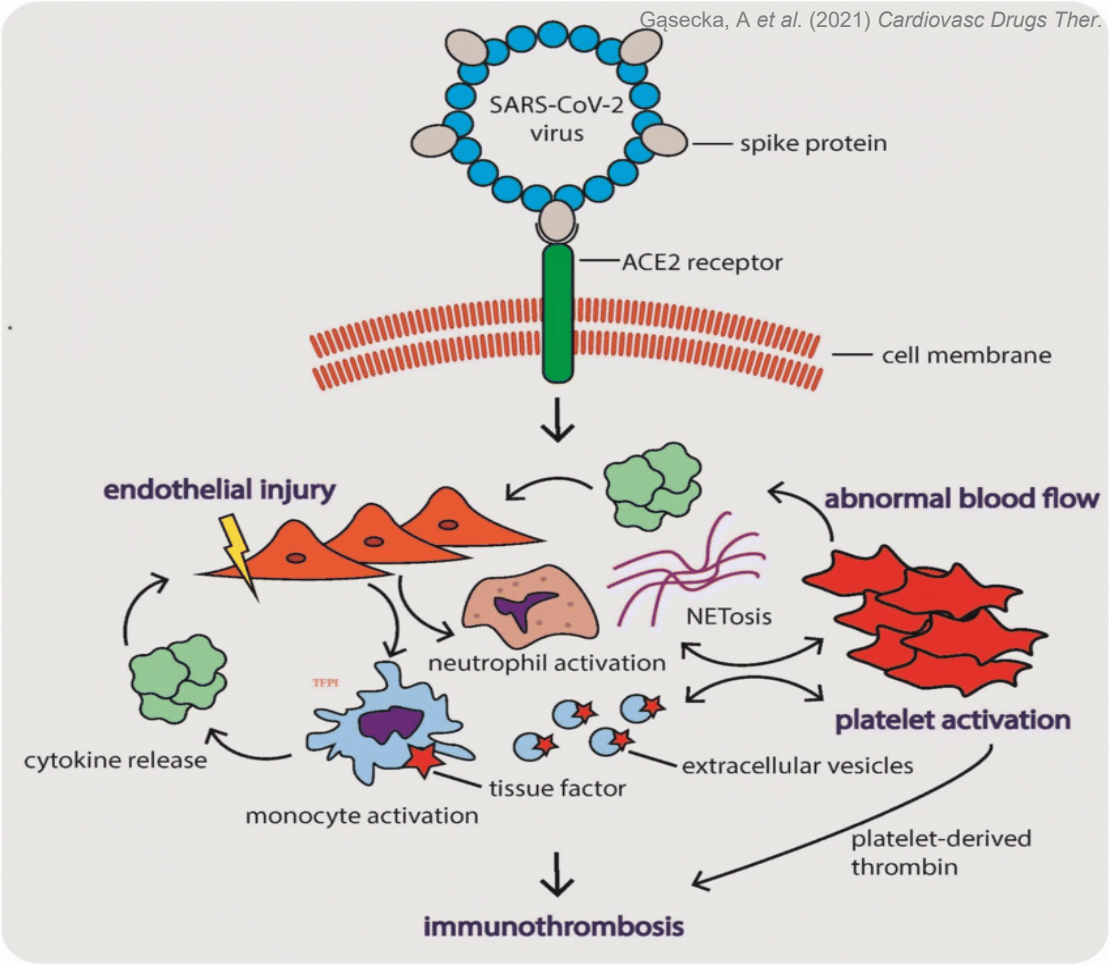
COVID and thrombosis

SARS-CoV-2 mechanism to form thrombus



Gemmati D, Bramanti B, Serino ML, Secchiero P, Zauli G, Tisato V (2020). COVID-19 and Individual Genetic Susceptibility/Repcetivity: Role of ACE1/ACe2 Genes, Immunity, Inflammation and Coagulation. Might the Double X-Chromosome in Females Be Protective against SARS-CoV2 Compared to the Single X-Chromosome in Male? nt. J. Mol. Sci. 2020, 21, 3474; doi:10.3390/ijms21103474

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Variants of concern

WHO defined VOC as variants with:

- ✓ Increased transmissibility or change epidemiology
- ✓ Increase in virulence or severity of symptoms
- ✓ Decreased effectiveness of treatments and vaccines or low diagnostic detection

Alpha	UK (Dec 2020)
Beta	South Africa (Dec 2020)
Gamma	Brazil (Jan 2021)
Delta	India (May 2021)
Omicron	Multiple (Nov 2021)

World Health Organization. Tracking SARS-CoV-2 variants. SARS-CoV-2 variants, working definitions and actions taken. Available at https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/ . Accessed [3/29/2022].

Goal

Report our experience as a COVID-19 referral center in the South Florida Region with thrombotic events due to COVID-19 infection before and during the Delta variant wave.

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Methods

Study participants

Retrospective chart review at UMH and JHS between June 2020 and August 2021.

Inclusion/Exclusion criteria

- > 18 years
- Admitted with confirmed COVID-19

- Had acute thrombotic event evidenced by US or CT scan

- During Delta Variant Wave

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Disease severity

Population

This recommendation applies only to people with these characteristics:

Disease severity

Non-severe	Severe	Critical
Absence of signs of severe or critical disease	Oxygen saturation <90% on room air	Requires life sustaining treatment
	Signs of pneumonia	Acute respiratory distress syndrome
	Signs of severe respiratory distress	Sepsis
		Septic shock

Infographic co-produced by the BMJ and MAGIC; designer Will Stahl-Timmins (see BMJ Rapid Recommendations).

WHO Therapeutics Steering Committee. Therapeutics and COVID-19. Living Guideline. WHO/2019-nCoV/therapeutics/2021.1 ed. World Health Organization 31 March 2021.

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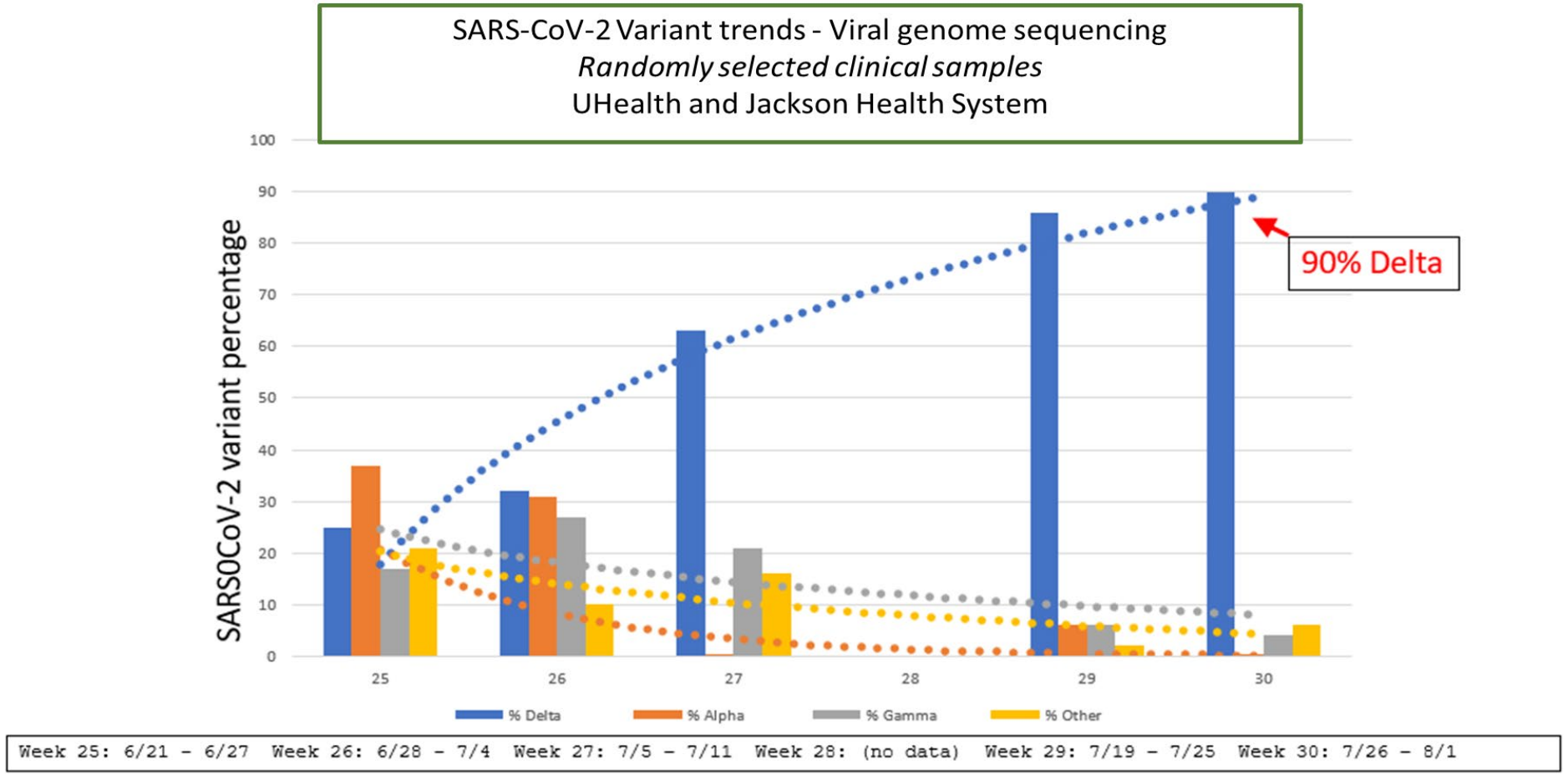
Figure 1. COVID-19 Delta variant peak compared to other variants.



6/1/2021 ⟷ 8/12/2021

90% Delta variant
50 pts

By: David Andrews, MD. Associate professor of clinical, department of Pathology, Division of clinical and translational research. Leonard M. Miller School of Medicine, University of Miami.

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Methods

Primary Outcomes:

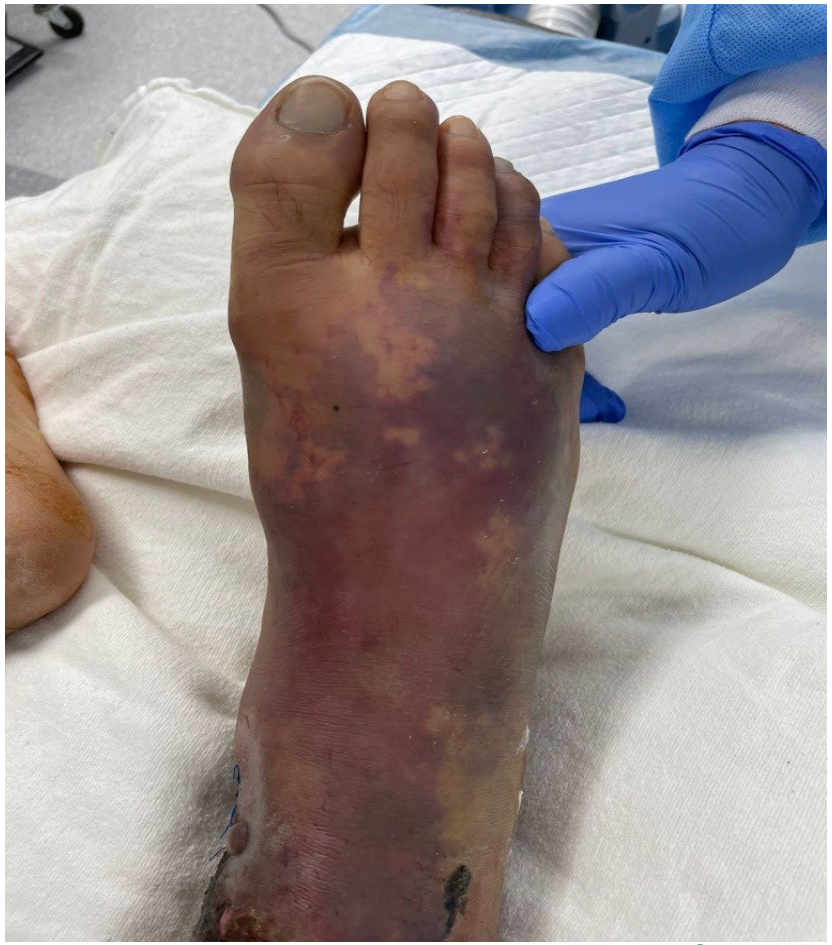
Descriptive analysis of thrombotic event related to COVID-19, comparing subjects during Delta variant wave (DW) and non-Delta (NDW):

- ✓ Venous thromboembolism (VTE)
- ✓ Arterial thromboembolism
- ✓ Pulmonary embolism (PE)
- ✓ Myocardial infarction (MI)
- ✓ Ischemic cerebral infarction.

Secondary Outcomes:

Associations of thrombotic events with additional factors:

- ✓ Demographic characteristics
- ✓ Anticoagulation strategies
- ✓ COVID-19 infection evolution



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Demographic characteristics and comorbidities compared between DW and NDW

	Non-Delta n=206	Delta n=50	P-value
Age – in years (SD)	66 (±10)	59 (±10)	**<0.001**
Sex – N (%)			0.78
Female	82 (40%)	21 (42%)	
Male	124 (60%)	29 (58%)	
Ethnicity – N (%)			0.25
Caucasian	3 (1%)	0 (0%)	
Hispanic	116 (56%)	23 (46%)	
African American	87 (42%)	27 (54%)	
BMI – kg/m² (SD)	30 (±5)	26 (±4)	**0.021**
Vaccination Status – N (%)			**0.002**
None	195 (95%)	45 (90%)	
One dose	0 (0%)	3 (6%)	
Two doses	11 (5%)	2 (4%)	
Smoking – N (%)			0.83
Never	152 (73%)	40 (80%)	
Former	17 (10%)	3 (7%)	
Current	8 (5%)	2 (4%)	
Comorbidities – N (%)			
Hypertension	143 (69%)	29 (58%)	0.12
Diabetes Mellitus	111 (54%)	21 (42%)	0.13
COPD	18 (9%)	3 (6%)	0.53
Asthma	19 (9%)	2 (4%)	0.23
CAD/CHF	45 (22%)	9 (18%)	0.55
Atrial Fibrillation	17 (8%)	0 (0%)	0.036
TIA/Stroke	6 (3%)	4 (8%)	0.096
Peripheral Arterial Disease	5 (2%)	2 (4%)	0.54
CKD	58 (28%)	12 (24%)	0.55
Active Malignancy	19 (9%)	2 (4%)	0.23
Thrombophilia	3 (1%)	1 (2%)	0.78
Immunosuppression	24 (12%)	7 (14%)	0.65
Previous DVT/PE	16 (8%)	8 (16%)	0.073
Start of COVID symptoms – in days* [IQR]	3 [1-7]	4 [1-7]	0.39

(*)Start of COVID symptoms in number of days prior to admission.

Thrombotic outcomes in the study cohort

	n=256
Venous Thrombosis – N (%)	153 (60%)
Upper extremity	30 (20%)
Lower extremity	101 (66%)
Upper and lower extremities	13 (8%)
Neck and thoracic veins	9 (6%)
Arterial Thrombosis – N (%)	60 (23%)
Upper extremity	8 (14%)
Lower extremity	47 (78%)
Upper and lower extremity	3 (5%)
Visceral thrombus	2 (3%)
Arterial and Venous Thrombosis – N (%)	43 (17%)
Pulmonary Embolism – N (%)	72 (28%)
Myocardial infarction – N (%)	14 (5%)
Aortic thrombus – N (%)	4 (2%)
Stroke – N (%)	3 (1%)
Multiple Thrombotic Locations* – N (%)	91 (35%)
Time of Thrombosis from admission – in days* [IQR]	4 [1-12]
Anticoagulation treatment – N (%)	228 (89%)
Start of anticoagulation – in days** [IQR]	2 [1-9]
DVT prophylaxis – N (%)	157 (61%)
Surgery – N (%)	30 (12%)
ICU – N (%)	195 (76%)
Deceased – N (%)	99 (39%)
D-dimer – in [IQR]	8 [3-20]
Fibrinogen – in [IQR]	383 [246-535]
PT – in [IQR]	15 [15-18]
aPTT – in [IQR]	38 [31-65]
Ferritin – in [IQR]	808 [398-1,409]
Antiphospholipid Antibody – in [IQR]	32 [1-35]

N: number; IQR: interquartile range; DVT: deep venous thrombosis; ICU: intensive care unit; IQR: interquartile range; PT: prothrombin time; aPTT: partial thromboplastin time.
(*)Time of thrombosis detection in days since hospital admission.
(**)Start of anticoagulation treatment in days since hospital admission.

Thrombotic events compared between DW and NDW

	non-Delta n=206	Delta n=50	P-value
Venous Thrombosis – N (%)	155 (75%)	41 (82%)	0.31
Arterial Thrombosis – N (%)	85 (41%)	18 (36%)	0.50
Thrombi location – N (%)			
Upper extremity	43 (21%)	11 (22%)	0.86
Lower extremity	131 (63%)	33 (66%)	0.75
Pulmonary Embolism	58 (28%)	14 (28%)	0.98
Myocardial Infarction	12 (6%)	2 (4%)	0.61
Aortic thrombi	3 (1%)	1 (2%)	0.78
Stroke	3 (1%)	0 (0%)	0.39
Multiple Thrombotic Locations*	74 (36%)	16 (32%)	0.60
Time of Thrombosis – in days* [IQR]	5 [1-11]	2 [1-13]	0.92
Anticoagulation treatment – N (%)	185 (90%)	44 (88%)	0.71
Start of anticoagulation – in days** [IQR]	2 [1-10]	1 [1-5]	0.22
DVT prophylaxis – N (%)	134 (65%)	23 (46%)	0.057
Surgery – N (%)	25 (12%)	5 (10%)	0.67
ICU – N (%)	157 (76%)	38 (76%)	0.97
Deceased – N (%)	78 (38%)	21 (42%)	0.61
D-dimer – in [IQR]	9 [3-2]	6 [3-13]	0.16
Fibrinogen – in [IQR]	384 [280-546]	355 [150-518]	0.29
PT – in [IQR]	15 [15-17]	16 [15-18]	0.33
aPTT – in [IQR]	37 [30 – 59]	50 [35-87]	0.008
Ferritin – in [IQR]	794 [412-1,365]	861 [327-1,892]	0.72

N: number; IQR: interquartile range; DVT: deep venous thrombosis; ICU: intensive care unit; IQR: interquartile range; PT: prothrombin time; aPTT: partial thromboplastin time.
(*) Time of thrombosis detection in days since hospital admission.
(**) Start of anticoagulation treatment in days since hospital admission.

Risk of thrombosis in DW

	Thrombotic events		
Variant	+	-	
DW	50	94	144
NDW	206	614	820

DW 34.7% thrombotic rate
NDW 25.1% thrombotic rate

Estimated 1.36 times higher risk of thrombosis in patients infected with COVID-19 during the DW than the NDW.

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Associated factors

Multiple regression models for thrombotic events:

P-value < 0.05 was considered significant.

- African Americans more likely to have **arterial** thromboembolism (OR: 1.78 [CI: 1.04 – 3.05] p=**0.035**)
- Immunosuppressed patients were less likely to have **arterial** thromboembolism (OR: 0.38 [CI: 0.15 – 0.96]. p=**0.042**)
- Females are more likely to present with **multiple** thrombi simultaneously (OR: 2.15 [CI: 1.20 – 3.85]. p=**0.009**)
- Active malignancy also presented with **multiple** thrombi (OR: 5.99 [CI: 2.14 – 16.78]. p=**0.001**)
- **D-dimer** was correlated with:
  - ✓ Lower extremity thrombosis (RR: 4.74 [CI: 1.96 – 7.53]. p=**0.001**)
  - ✓ PE (RR: 5.63 [CI: 2.13 – 9.14]. p=**0.002**)
  - ✓ Longer ICU length of stay (RR: 4.79 [CI: 2.47 – 7.13]. p**<0.001**).

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Anticoagulation and DVT prophylaxis

		Non-Delta n=206	Delta n=50	p-value
Anticoagulation Agent – N (%)	Heparin drip	106 (51.4%)	20 (40%)	0.32
	Enoxaparin	49 (23.8%)	16 (32%)	
	Warfarin	2 (0.9%)	1 (2%)	
	Rivaroxaban	2 (0.9%)	1 (2%)	
	Apixaban	21 (10.1%)	8 (16%)	
DVT prophylaxis – N (%)	Heparin SQ	75 (36.5%)	12 (24%)	0.98
	Enoxaparin SQ	58 (28%)	10 (20%)	
	Fondaparinux	1 (0.4%)	1 (2%)	
Aspirin – N (%)		54 (26%)	16 (32%)	0.38
Discharge Anticoagulation Agent – N (%)	Heparin drip	11 (5%)	1 (2%)	0.14
	Enoxaparin	17 (8%)	8 (16%)	
	Warfarin	8 (3%)	3 (6%)	
	Rivaroxaban	5 (2%)	1 (2%)	
	Apixaban	73 (35%)	14 (28%)	
	Argatroban	2 (0.9%)	1 (2%)	

N: number; SQ: subcutaneous; DVT: deep venous thrombosis.

(*) Patients not reported on discharge anticoagulation expired, had the AC stopped due to drop in hemoglobin or documented bleeding, or were never placed on AC due to prior contraindications.

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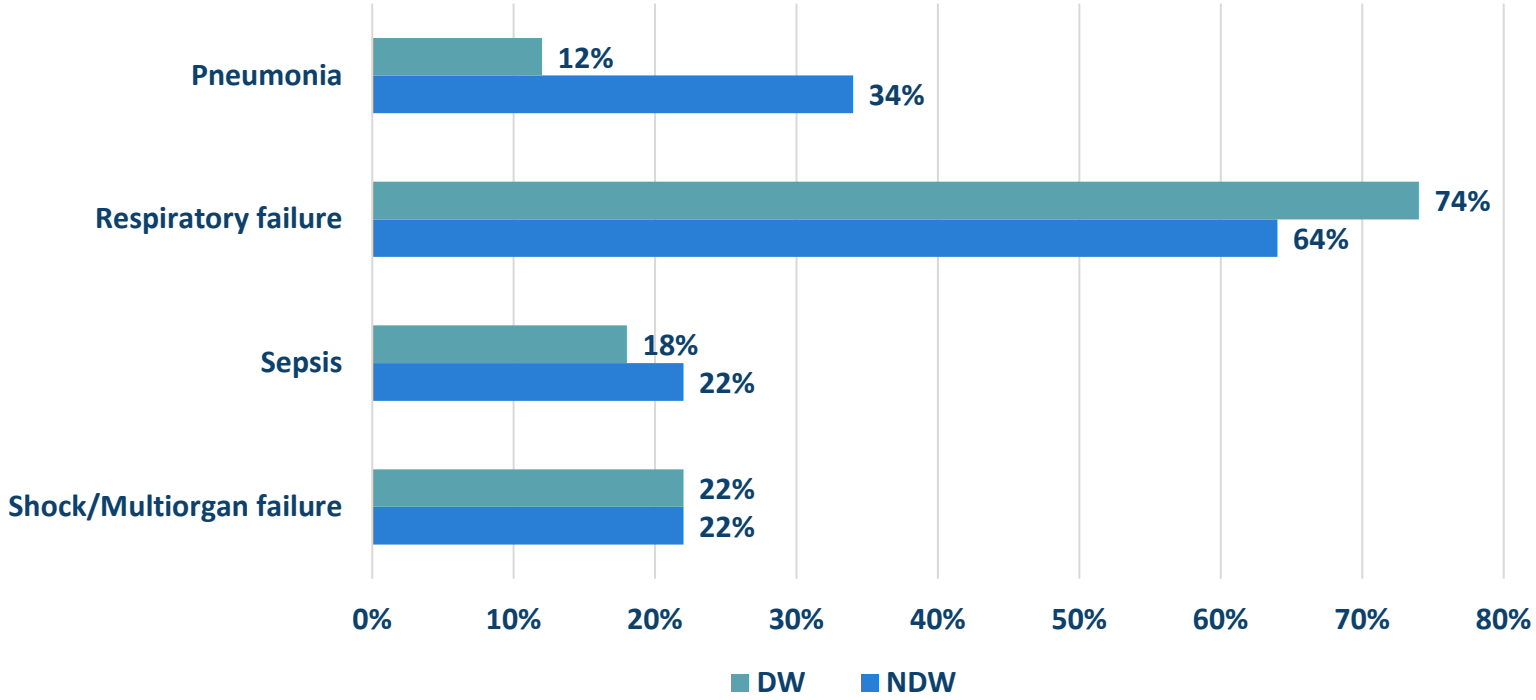
Other complications DW Vs. NDW



Complications secondary to COVID-19 infection comparing Delta wave (DW) to NDW (non-Delta wave)

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Highlights

- 26.5% of the patients admitted with COVID-19 positive test presented with thrombotic events confirmed by US or CTA in a median of 4 days since the admission. (Klok et al. Thrombosis research, 2020)
- We reported similar rates of VTE, lower PE and higher arterial thromboembolism, compared to literature available (Malas et al. Clinical Medicine, 2020)
- Some studies report correlation between the D-dimer levels and the severity of COVID-19 disease. (Militades et al. J Neurosug Anesthesiology, 2022)
- Patients on early DVT prophylaxis still presented with thrombotic complications despite adequate preventative measures. (Oba et al. Front Cardiovasc Med, 2021)
- Limitations:
  - ✓ Generalizability: population distribution and patient selection
  - ✓ Retrospective nature
  - ✓ Uncertainty

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Genetic susceptibility

The major genetic risk factor for severe COVID-19 is inherited from Neanderthals

Hugo Zeberg ✉ & Svante Pääbo ✉

Nature **587**, 610–612 (2020) | Cite this article

Multi-ancestry fine mapping implicates *OAS1* splicing in risk of severe COVID-19

Jennifer E. Huffman, Guillaume Butler-Laporte, Atlas Khan, Erola Pairo-Castineira, Theodore G. Drivas, Gina M. Peloso, Tomoko Nakanishi, COVID-19 Host Genetics Initiative, Andrea Ganna, Anurag Verma, J. Kenneth Baillie, Krzysztof Kiryluk, J. Brent Richards & Hugo Zeberg ✉

Nature Genetics **54**, 125–127 (2022) | Cite this article

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Current treatment guidelines

February 2022 FDA issued a EUA for monoclonal antibodies anti-SARS-CoV-2

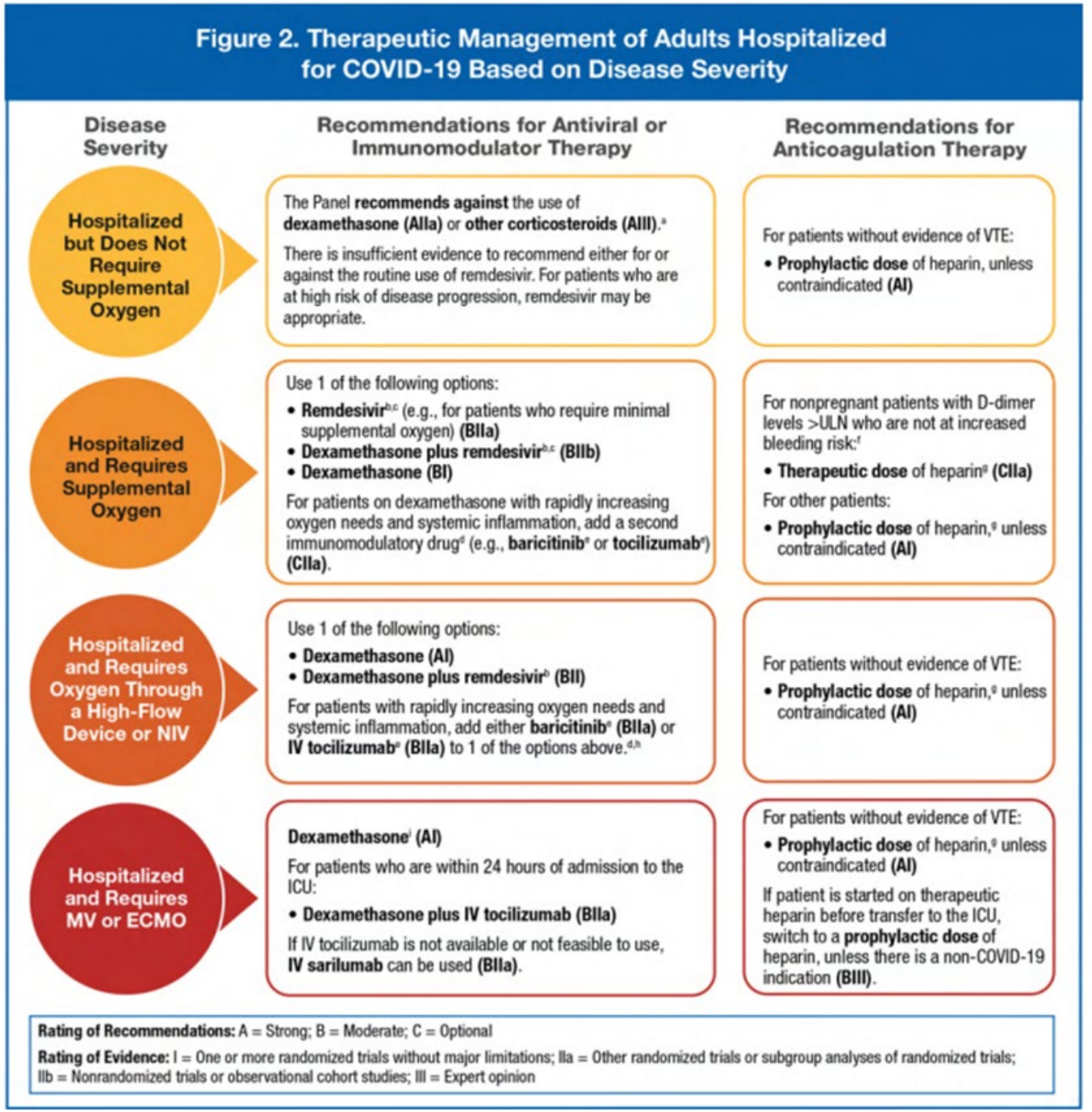

Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., **baricitinib**[e] or **tocilizumab**[e]) **(CIIa)**.	For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk:[f] • **Therapeutic dose** of heparin[g] **(CIIa)** For other patients: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BII)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the options above.[d,h]	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone**[i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)** If patient is started on therapeutic heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [3/29/2022].

Conclusions

- Our experience as a referral center in the South Florida Region, shows that our patient population presents high rates of thrombotic complications secondary to COVID-19.
- The majority of the patients presenting with complications were not vaccinated.
- Patients admitted during the delta wave showed an elevated risk for thrombotic complications
- A high level of suspicion, awareness and more evidence to standardize anticoagulation strategies is needed.

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