Azienda Ospedaliero Universitaria Careggi

UNIVERSITÀ DEGLI STUDI FIRENZE

Nona Giornata Fiorentina dedicata ai pazienti con malattie mieloproliferative croniche

Sabato 20 maggio 2023

Cosa ha insegnato la pandemia COVID

Tiziano BARBUI
Fondazione FROM- Ospedale di Bergamo

Cosa ha insegnato la pandemia COVID-19

1. Fragilità dei sistemi sanitari di fronte alla pandemia
2. Come hanno reagito i ricercatori (di base, clinici, industria…)
3. La collaborazione multicentrica particolarmente nelle malattie rare: esempio: il Covid nelle MPN
4. La nuova normalità

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Coronavirus, l’atto di nascita: 17 novembre 2019, provincia dell’Hubei, Cina.

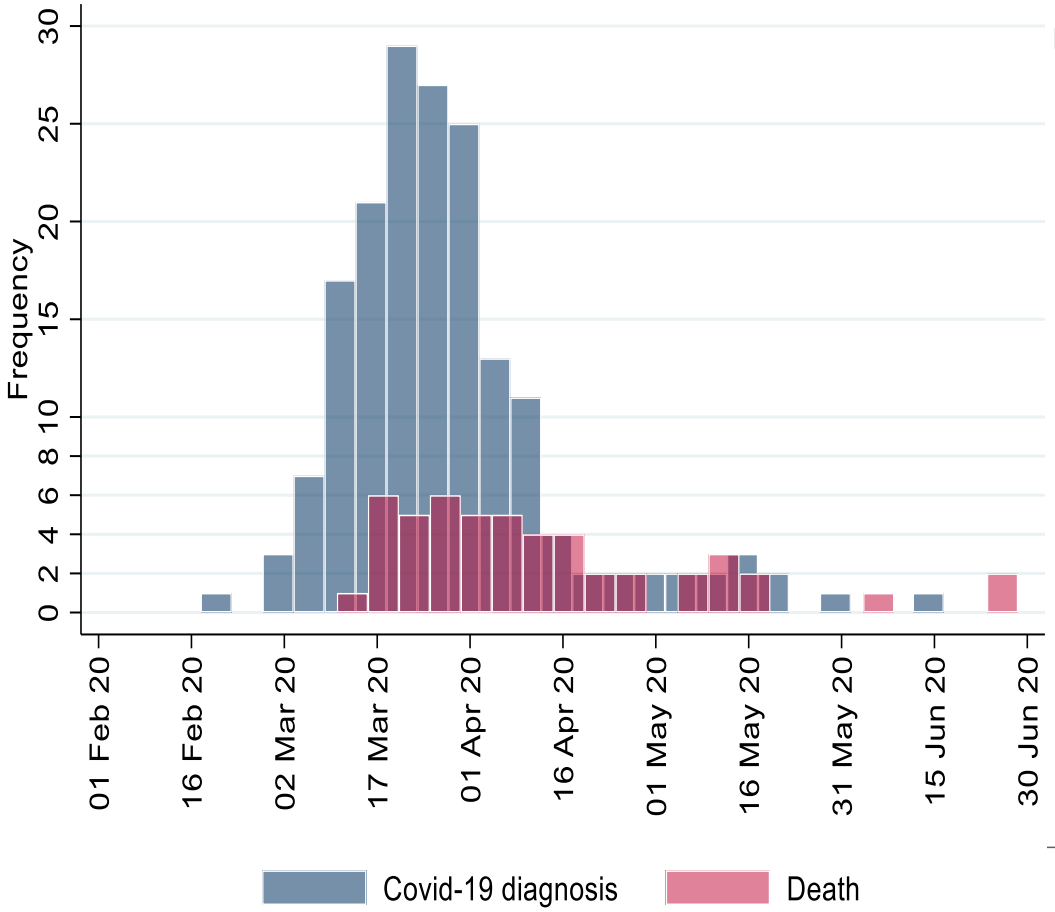
Il **primo caso di contagio** accertato da Covid-19, la misteriosa polmonite provocata dal nuovo coronavirus, può essere fatto risalire allo scorso **17 novembre**.

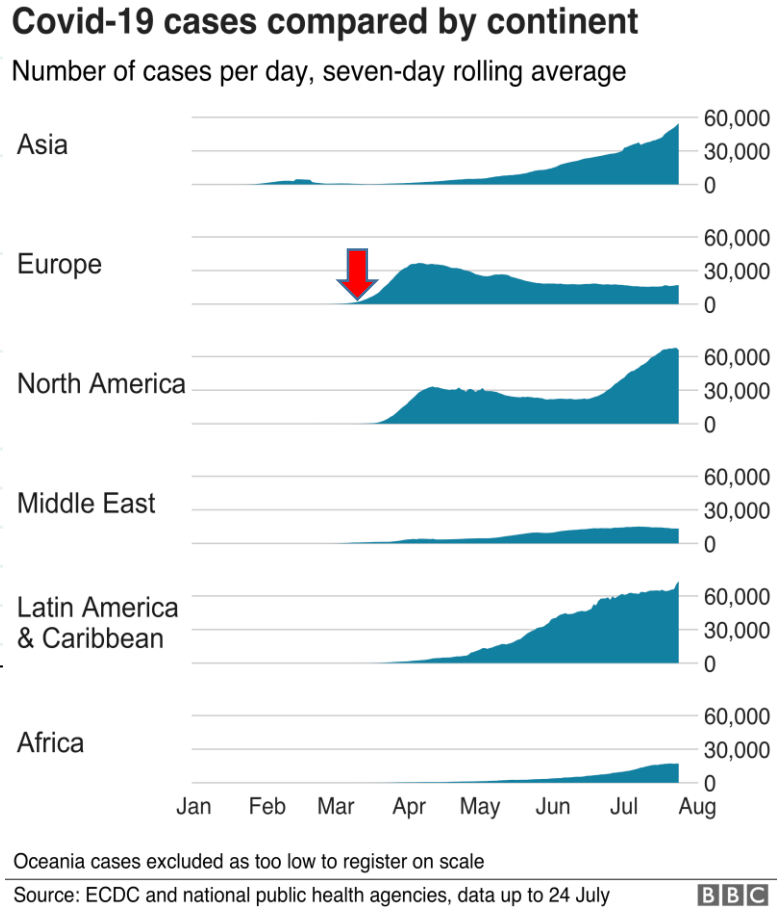
Il **paziente numero uno è un 55 enne dell’Hubei**, la provincia di Wuhan, che ha quindi contratto l’infezione **due settimane prima del 1 dicembre 2019.**

A fine anno la notizia circola già sui social.
Il dr Li Wenliang, medico dell’università di Wuhan che scrive in un post che contagi sono dovuti a un virus del tipo SARS (30 dicembre), viene ufficialmente richiamato e arrestato. Scagionato, morirà poi per le conseguenze dell’infezione.

Per due mesi le autorità cinesi hanno cercato di ignorare il problema, insabbiando tutti gli allarmi che arrivavano dagli ospedali di Wuhan.

Insorgenza e diffusione della pandemia





Bergamo ha avuto il più alto tasso di decessi: sei volte di più rispetto al 2019

A marzo 2020 in provincia di Bergamo sono morte più di 5.400 persone (1,2 milioni), di cui 4.500 per coronavirus.

Le immagini dei mezzi militari che trasportavano centinaia di bare e le pagine dei necrologi de L'Eco si sono diffuse in tutto il mondo, testimoniando la tragedia che tutti i bergamaschi stavano vivendo.

At the Epicenter of the Covid-19 Pandemic and Humanitarian Crises in Italy: Changing Perspectives on Preparation and Mitigation

Authors: Mirco Nacoti, , Andrea Ciocca, Angelo Giupponi, MD, Pietro Brambillasca, MD, Federico Lussana, MD , Michele Pisano, MD, Giuseppe Goisis, PhD, and Carlo Montaguti, MDAuthor Info & Affiliations . NEJM March 21, 2020

Il nostro ospedale è altamente contaminato e siamo ben oltre il punto di non ritorno: **300 posti letto su 900 sono occupate da malati di Covid-19**. Ben il **70% dei letti di terapia intensiva** nel nostro ospedale è riservato a pazienti gravemente malati di Covid-19 con una ragionevole possibilità di sopravvivere.

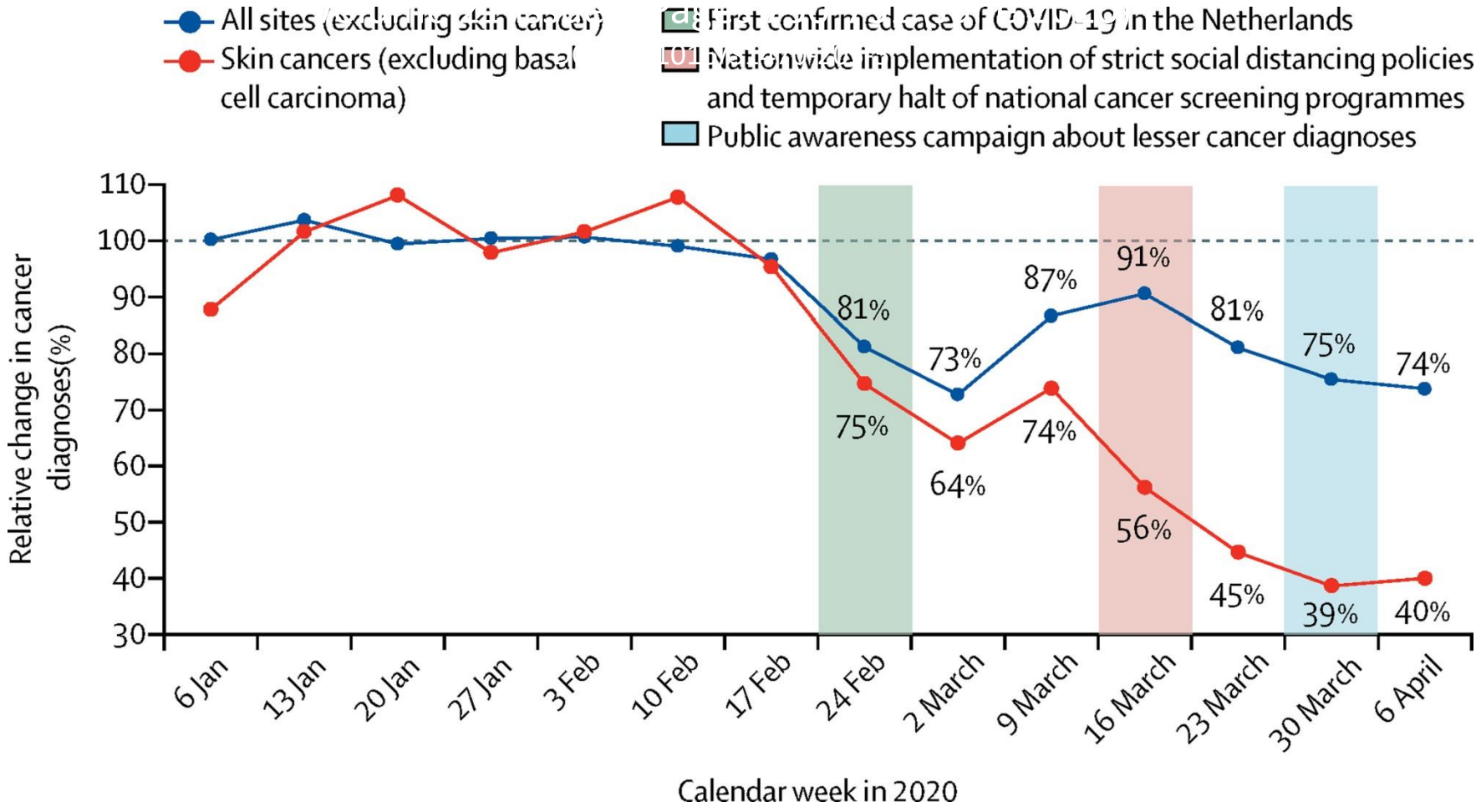
I pazienti più anziani non vengono rianimati e muoiono da soli senza adeguate cure palliative, mentre la famiglia viene avvisata per telefono, spesso da persone ben intenzionate, esauste ed emotivamente medico impoverito senza alcun contatto precedente.

Questo focolaio è un problema di salute pubblica e umanitario. Richiede scienziati sociali, epidemiologi, esperti di logistica, psicologi e lavoratori sociali. Abbiamo urgente bisogno di agenzie umanitarie che riconoscano l'importanza del locale fidanzamento.

L'OMS ha dichiarato profonda preoccupazione per la diffusione e la gravità della pandemia e sui livelli allarmanti di inerzia. Tuttavia, sono necessarie misure coraggiose per rallentare il infezione. Il blocco è fondamentale: **il distanziamento sociale ha ridotto la trasmissione di circa il 60% in Cina.**

Il coronavirus è l'Ebola dei ricchi e richiede uno sforzo transnazionale coordinato.

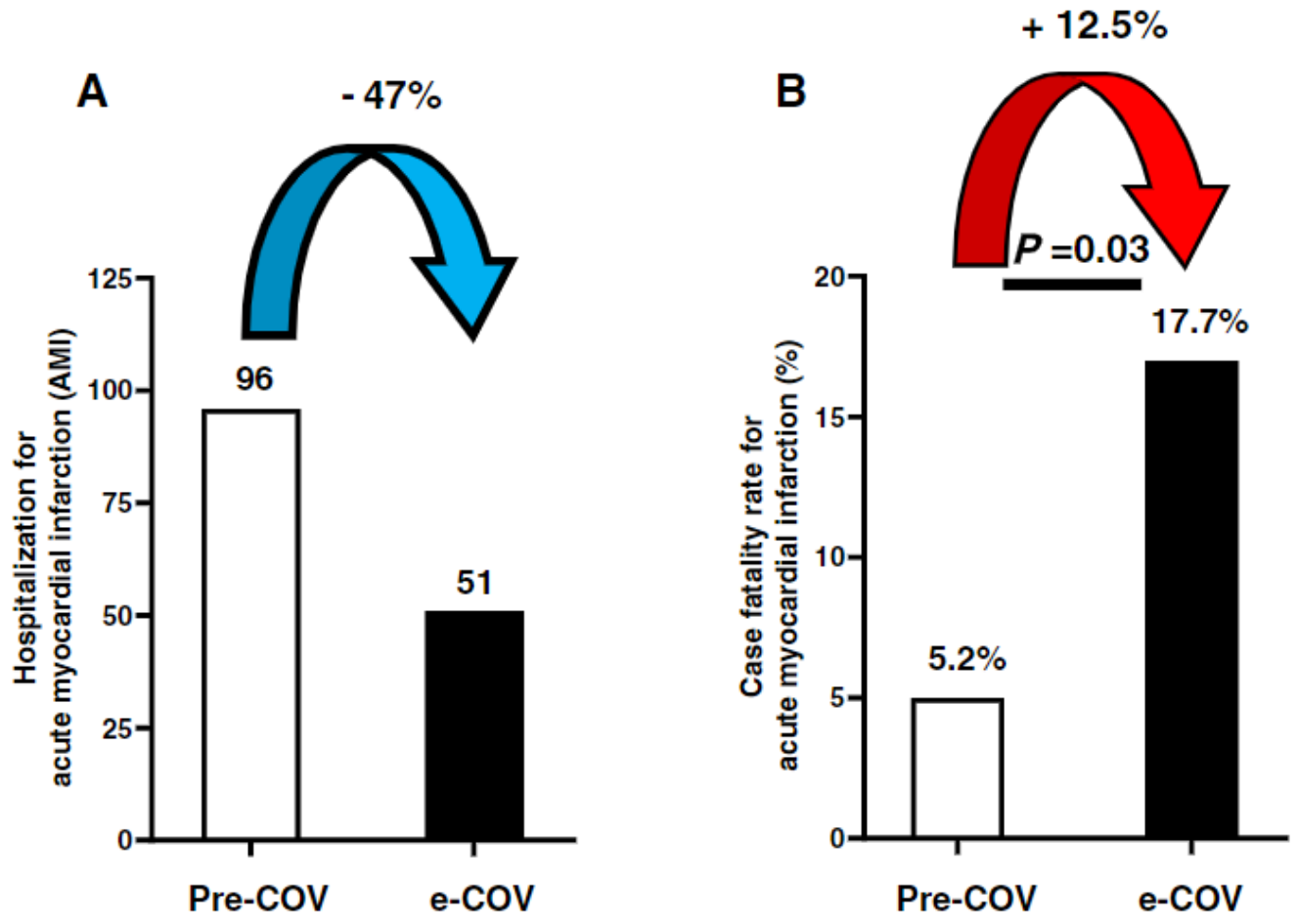
Meno diagnosi di tumore durante il COVID (Olanda)



The Lancet Oncology
Volume 21 Issue 6 Pages 750-751 (June 2020)
DOI: 10.1016/S1470-2045(20)30265-5

Reduced hospitalization for acute myocardial infarction and increased mortality during earlyCOVID-19 pandemic

Department of Internal Medicine and Cardiology, Charité—Universitätsmedizin Berlin, Published online 6 December 2020 in Wiley Online Library



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Come la comunità della ricerca medica ha risposto a COVID-19
La nuova norma dell'editoria: la quantità sulla qualità

Definizione di una prestampa (PREPRINT)

Una prestampa è una bozza completa di un documento di ricerca che viene condiviso pubblicamente prima di essere sottoposto a peer-review. Alla maggior parte dei preprint viene assegnato un identificatore di oggetto digitale (DOI) in modo che possano essere citati in altri documenti di ricerca.

Sottomissione a una rivista: la sottomissione **è in fase di verifica editoriale interna. Nella maggior parte dei casi, ciò richiederà meno di 24 ore** . Se accettato, non è richiesta alcuna azione da parte degli autori.

Una prestampa è una bozza completa di un documento di ricerca che viene condivisa pubblicamente prima che sia stata sottoposta a revisione paritaria.

GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia

Luis Corral-Gudino[1], Alberto Bahamonde[2], Francisco Arnaiz-Revillas[3], Julia Gómez-Barquero[4], Jesica Abadía-Otero[4], Carmen García-Ibarbia[5], Víctor Mora[6], Ana Cerezo-Hernández[7], José L. Hernández[5], Graciela López-Muñíz[7], Fernando Hernández-Blanco [2], Jose M. Cifrián[6], Jose M. Olmos[5], Miguel Carrascosa[8], Luis Nieto[9], María Carmen Fariñas[3], and José A. Riancho[5], for the GLUCOCOVID investigators*

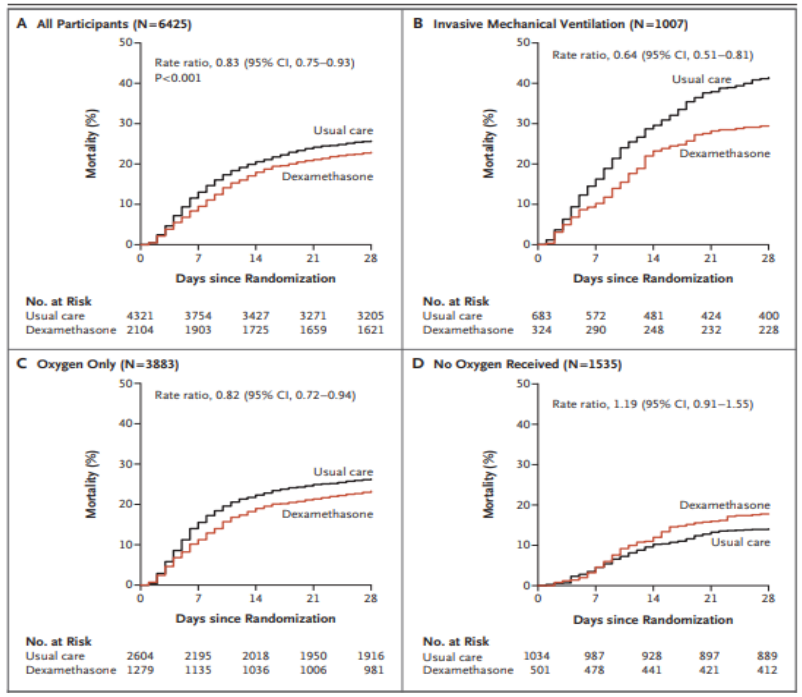
Conclusions A short course of MP **had a beneficial effect on the clinical outcome of severe COVID-19 pneumonia,** decreasing the risk of the composite end point of admission to ICU, NIV or death.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*



CONCLUSIONS

In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality **among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.**

(Funded by the Medical Research Council and National Institute for Health Research and others; **RECOVERY ClinicalTrials.gov number,** NCT04381936; ISRCTN number, 50189673.)

Corral L, Bahamonde A, Arnaiz delas Revillas F, et al. GLUCOCOVID: a controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. **June 18, 2020** (https://www .medrxiv.org/content/10.1101/2020.06.17 .20133579v1). preprint

This article was published on July 17, 2020, at NEJM.org

ORIGINAL ARTICLE

Meta-Analysis of Glucocorticoids for Covid-19 Patients Not Receiving Oxygen

Authors: Remo Daniel Covello, M.D., Laura Pasin, M.D., Stefano Fresilli, M.D., Krisztina Tóth, M.D., Caterina Damiani, M.D., Ludhmila Abrahão Hajjar, M.D., Ph.D., Alberto Zangrillo, M.D., and Giovanni Landoni, M.D. Author Info & Affiliations

Published April 18, 2023 | NEJM Evid 2023;2(5) | DOI: 10.1056/EVIDoa2200283 | VOL. 2 NO. 5

This meta-analysis shows that administering glucocorticoids in hospitalized patients with Covid-19 not receiving oxygen is likely associated with worse clinical outcomes.

Scope, quality, and inclusivity of clinical guidelines produced early in the covid-19 pandemic: rapid review

Andrew Dagens,[1] Louise Sigfrid,[1] Erhui Cai,[1] Sam Lipworth,[2] Vincent Cheung,[3] Eli Harris,[4] Peter Bannister,[5] Ishmeala Rigby,[5] Peter Horby[1]

Accepted: 13 May 2020

WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical guidelines produced in previous healthcare emergencies have fallen below gold standards of guideline development

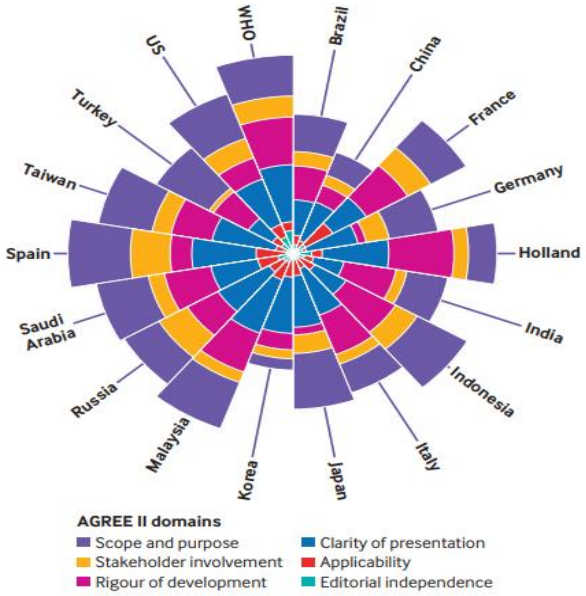
During the early coronavirus pandemic, a high degree of uncertainty existed about the optimal clinical management of patients with covid-19

WHAT THIS STUDY ADDS

Clinical guidelines written in the early covid-19 pandemic possessed methodological weaknesses, especially in the rigour of their development

Recommendations for the management of vulnerable groups such as older people were also neglected

Guidelines produced early in future pandemics should prioritise contingency, adaptability, and methodological rigour



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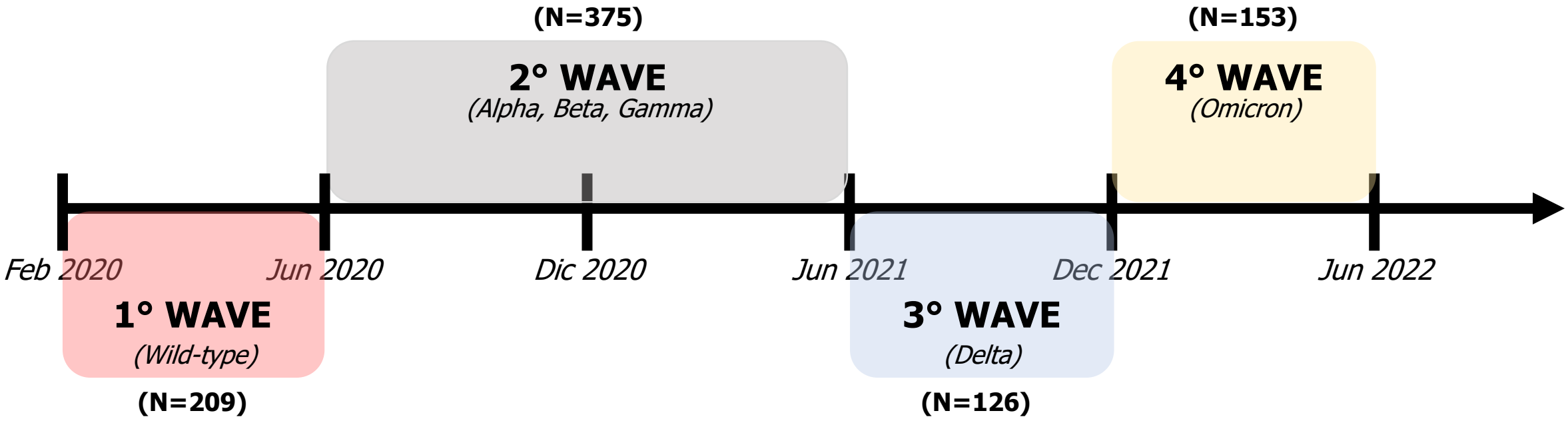
MPN-COVID study

(ClinicalTrials.gov: NCT04385160)

- **MPN-COVID study** was launched by *European LeukemiaNet (ELN)* in March 2020.
- **Participating Centers** (n=42) from Italy, Spain, Germany, France, Croatia, Poland, UK, Bulgaria
- **Total number of patients enrolled**: 863.



1. Barbui et al, ***High mortality rate in COVID-19 patients with myeloproliferative neoplasms after abrupt withdrawal of ruxolitinib.*** Leukemia, 2021
2. Barbui et al, ***Among classic myeloproliferative neoplasms, essential thrombocythemia is associated with the greatest risk of venous thromboembolism during COVID-19***. Blood Cancer Journal, 2021
3. Barbui et al, ***Long-term follow-up of recovered MPN patients with COVID-19***. Blood Cancer Journal, 2021

COVID-19 and Myeloproliferative Neoplasms: Frequently Asked Questions

Version 3.0; last reviewed July 20, 2020

The United States and countries around the world face a major public health concern with the current outbreak of the novel (new) coronavirus (COVID-19). **In an effort to serve its members, ASH is maintaining this webpage as a medium to exchange information to assist hematologists in navigating the COVID-19 public health crisis.**

Input from *Drs. Ruben Mesa, Alberto Alvarez-Larran, Claire Harrison, Jean-Jacques Kiladjian,* ***Alessandro Rambaldi,*** *Ayalew Tefferi,* ***Alessandro Vannucchi****, Srdan Verstovsek,* ***Valerio De Stefano, and Tiziano Barbui***

Le domande più frequenti dei pazienti con PV,ET,MF

I pazienti con MPN sono a più alto rischio di infezioni

Tra gli MPN, qual è il più vulnerabile?

I farmaci per controllare la proliferazione MPN possono aumentare il rischio di infezioni?

La fase acuta dell'infezione da SARS-CoV-2 in MPN

I pazienti MPN sono un gruppo ad alto rischio di morire per COVID-19?

I pazienti con MPN sono ad alto rischio di trombosi durante la fase acuta dell'infezione?

Vaccini per COVID-19 in MPN

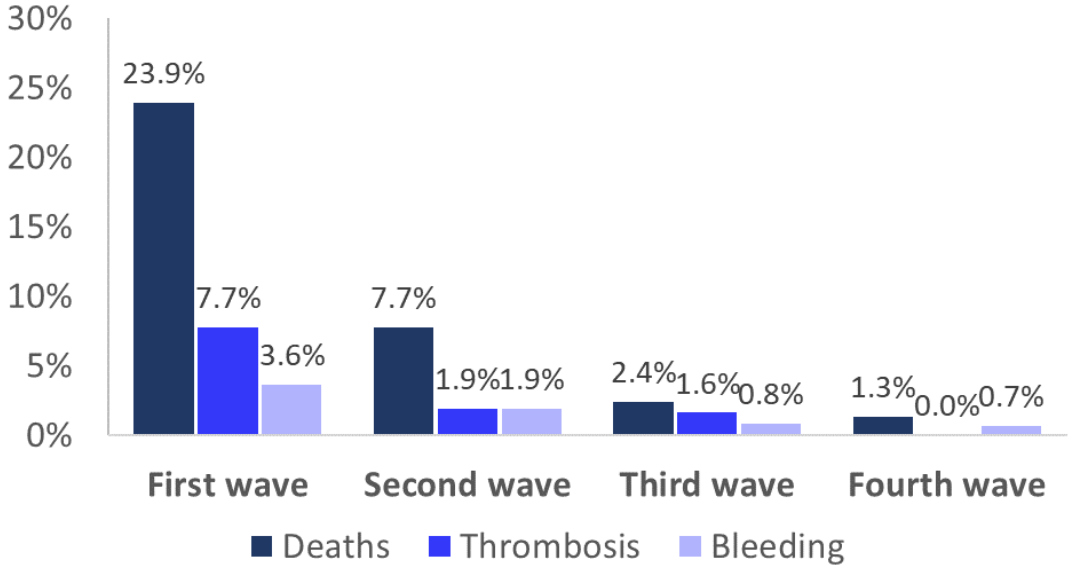
Le persone con MPN dovrebbero essere vaccinate contro il COVID-19?

Ci sono vaccini COVID-19 che dovrebbero essere evitati per le persone con MPN?

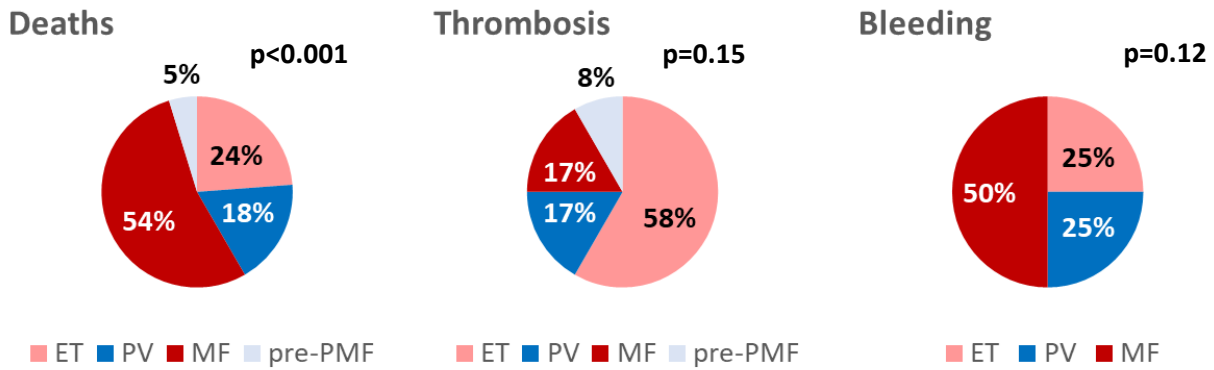
In che modo i farmaci per MPN influiscono sulla sicurezza e sull'efficacia dei vaccini COVID-19?

COVID-19 acute phase (within 70 days of COVID -19 diagnosis)

Acute phase Covid-19 outcomes over the four waves

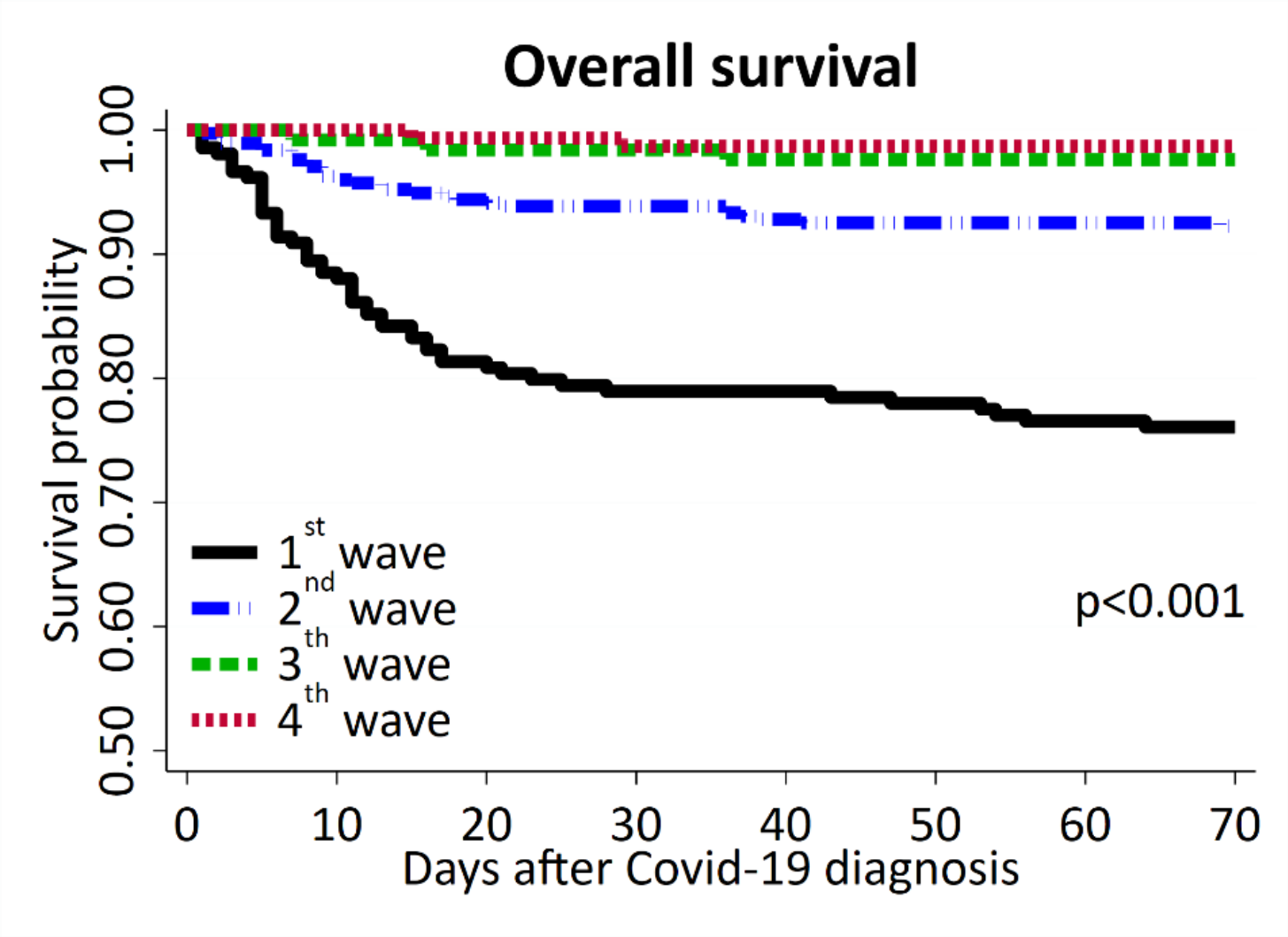


	FIRST WAVE (Wild-type)	SECOND WAVE (Alpha, Beta, Gamma)	THIRD WAVE (Delta)	FOURTH WAVE (Omicron)	p
	N=209	N=375	N=126	N=153	
Death	50/209 (23.9%)	29/375 (7.7%)	3/126 (2.4%)	2/153 (1.3%)	<0.001
Thrombosis	15/194 (7.7%)	7/368 (1.9%)	2/124 (1.6%)	0/152 (0.0%)	<0.001
Bleeding	7/194 (3.6%)	7/370 (1.9%)	1/124 (0.8%)	1/152 (0.7%)	0.22



Covid-19 acute phase outcomes

(Whitin 70 days of COVID -19 diagnosis)

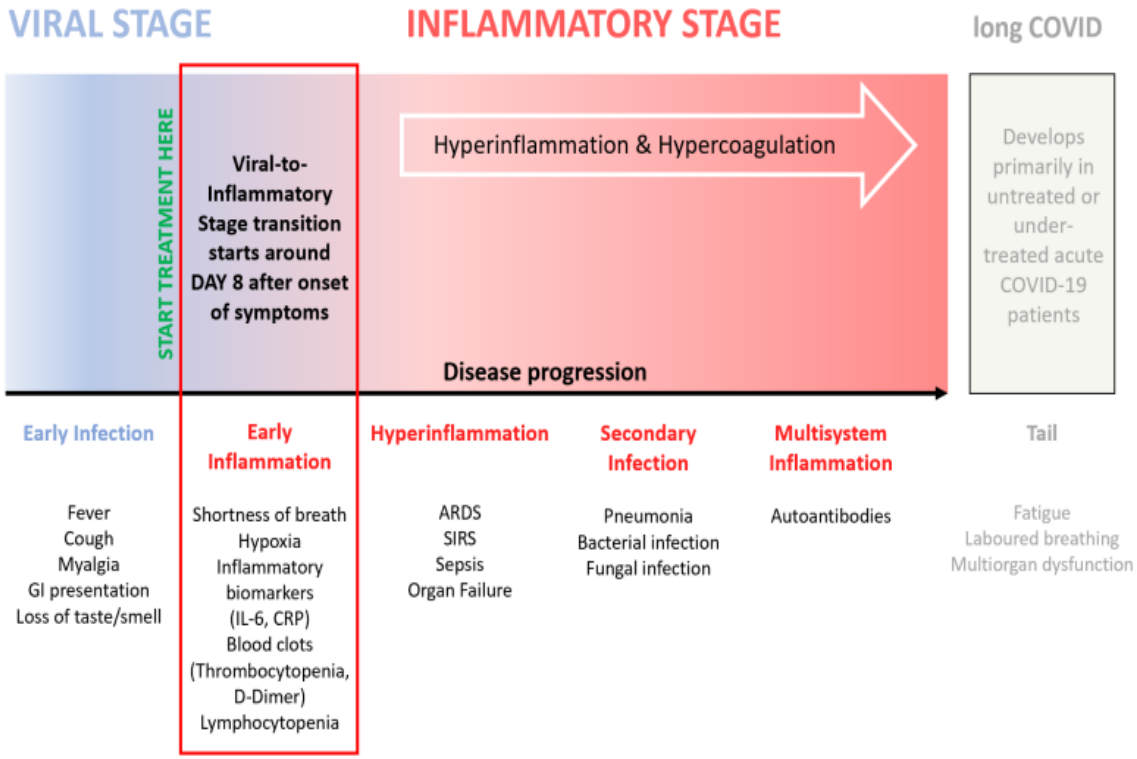


Quali insegnamenti per i pazienti che si ammalano di COVID-19 oggi e che non vengono ricoverati

Nei primi giorni della malattia (malattie live o moderata)

(i) Anticorpi monoclonali anti spike che prevengono la penetrazione del virus nelle cellule . Dato che Omicron h molte variant la loro attività è attualmente ridotta.

(ii) Gli antivirali Nirmatrelvir-ritonavir, Molnupiravir e remdesivir utilizziamo come target regioni virali conserva e ci si aspetta che possano rimanere attivi anche contro le mutazioni continue di OMICRON



Gandhi RT and Malani PN, JAMA 2022
Gandhi RT, Lynch JB, Del Rio C. Mild or moderate Covid-19. *N Engl J Med*. 2020;383(18):1757-1766.

Factors potentially associated with decline of mortality after the 1° COVID-19 wave

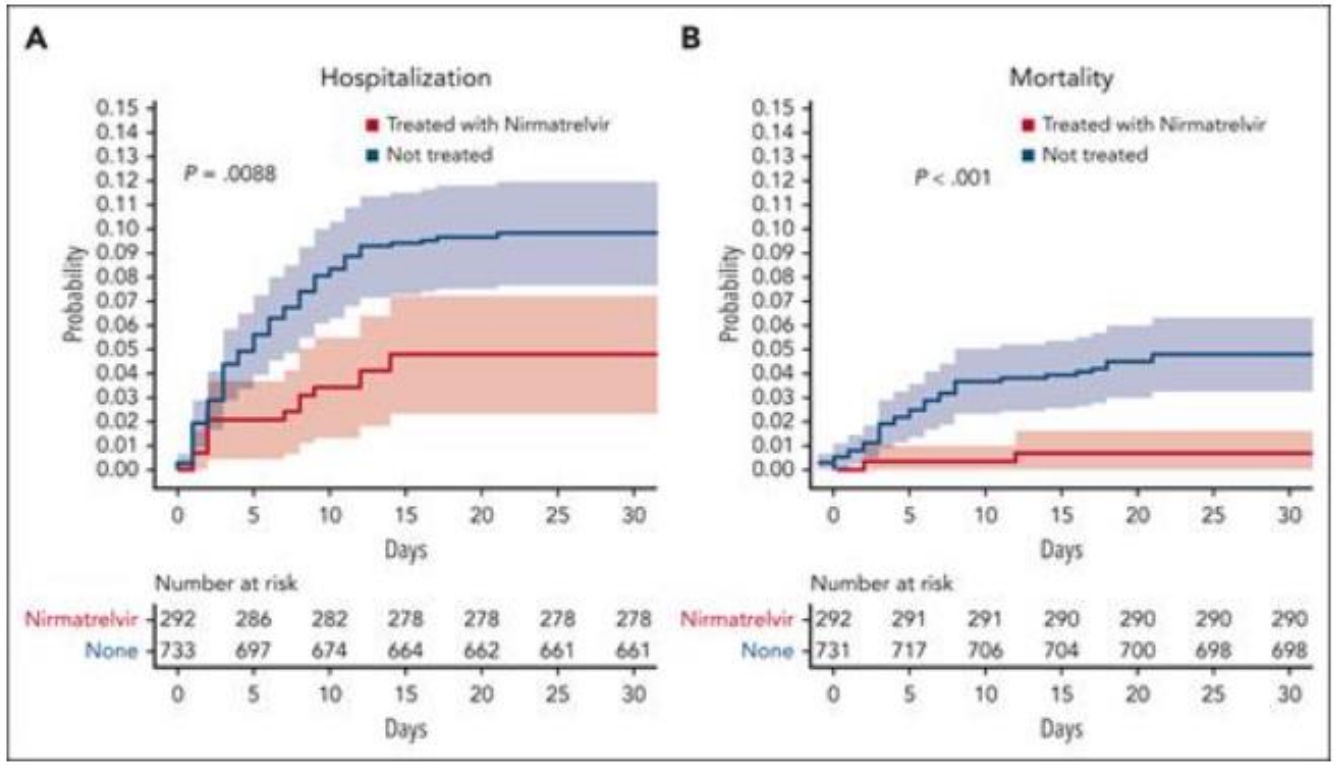
- Better healthcare organization
- Changes in patient's characteristics with different predictors of mortality (younger patients and lower proportion of cases with MF)
- Presence of less virulence circulating VOCs **causing a less intensive inflammatory responses**
- **Role of antiviral drugs, anti-inflammatory agents and vaccination**

Predictors of mortality in 202 MPN patients hospitalized for COVID-19* during the first 2 waves

Covariate	HR (95% Confidence interval)	P-value
Male sex	2.3 (1.2-4.2)	0.008
Age > 70 years	2.2 (1.2-4.4)	0.017
MF diagnosis	1.7 (0.9-3.1)	0.079
Ruxolitinib during-Covid	1.5 (0.8-3.0)	0.201
Respiratory intervention	4.7 (1.8-12.0)	0.001
Remdesivir	**0.1 (0.0-1.0)**	**0.055**
LMW heparin	0.4 (0.2-0.7)	0.003

* Deaths n=52; Excluded deaths from Ruxolitinib discontination

Effectiveness of nirmatrelvir plus ritonavir treatment for patients with chronic lymphocytic leukemia during the Omicron surge



Tadmor et al, Blood Vol 141, May 4, 2023

Intrinsic and treatment-induced immune dysfunction makes infections the major cause of death for patients with chronic lymphocytic leukemia (CLL) requiring therapy.

In a retrospective study, Tadmor et al report on the **positive impact of antiviral treatment for patients with CLL testing positive for SARS-CoV-2 infection, with lower risks of death and hospitalization**, particularly in patients over 65 years of age.

Immediate COVID-19 treatment in CLL appears to benefit these patients.

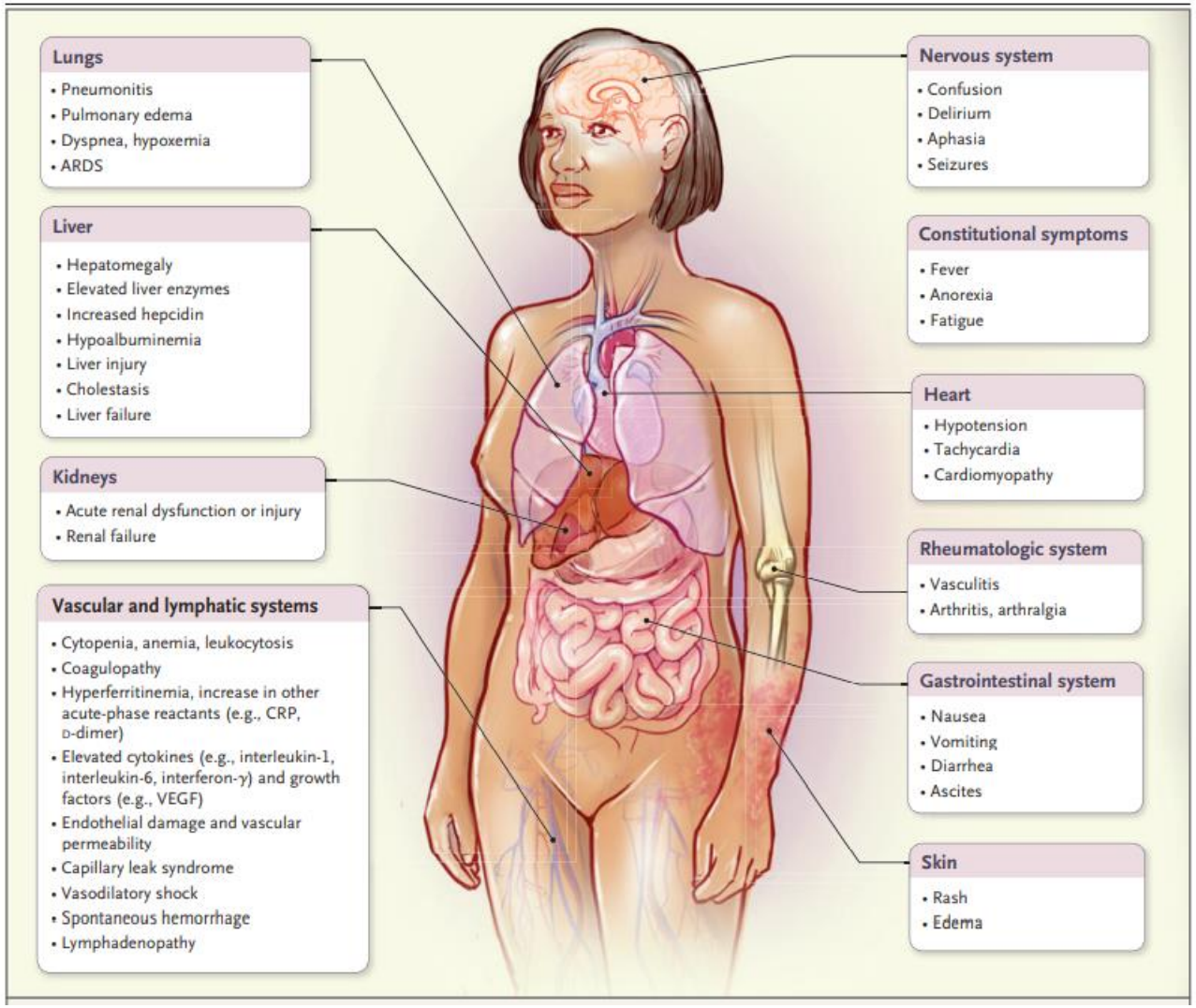
Hyperinflammation

Definition

«**Acute systemic inflammatory symptoms**, **and secondary organ dysfunction** due to inflammation which could be attributed to a normal response to a pathogen (if a pathogen is present), **or any cytokine-driven organ dysfunction (if no pathogen is present)»**

David C. Fajgenbaum, and Carl H. June, M.D N Engl J Med 2020;383:2255-73.

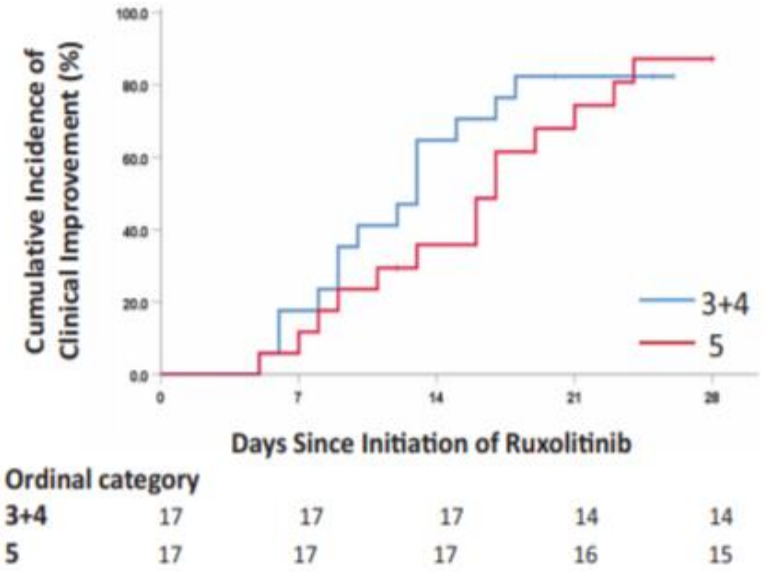
Hyperinflammation and Cytokine Storm

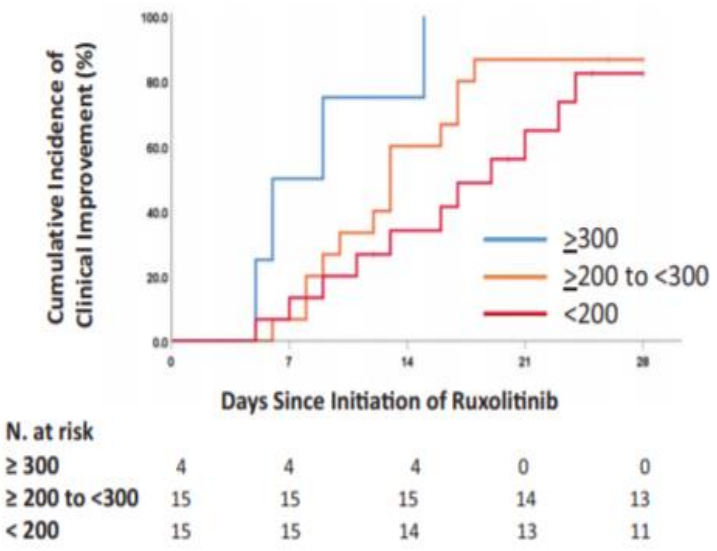


David C. Fajgenbaum, and Carl H. June, M.D N Engl J Med 2020;383:2255-73.

- **Graft Versus Host Disease**
- **Severe Infection**
  - Epstein-Barr virus (EBV)-associated hemophagocytic lymphohistiocytosis (EBV-HLH) and primary Hemaphagocytic Lymphohistiocytosis
  - **COVID-19 SARS-CoV-2 Infection in a susceptible person**
- **Immunotherapy (**CAR-T therapy; chimeric monoclonal anti-CD20 antibody rituximab , blinatumomab , nivolumab ,brentuximab etc…
- **RT Regimens for cancer**
- **VEXAS syndrome (2020, NEJM)** is a monogenic disease of adulthood males caused by somatic mutations in *UBA1* in hematopoietic progenitor cells. Inflammatpry symptoms that mimic rheumatic diseases and hematologic conditions (MDS, MGUS). Ruxo efficaceus, in some pts bone marrow transplant.

Compassionate use of JAK1/2 inhibitor ruxolitinib for severe COVID-19: a prospective observational study





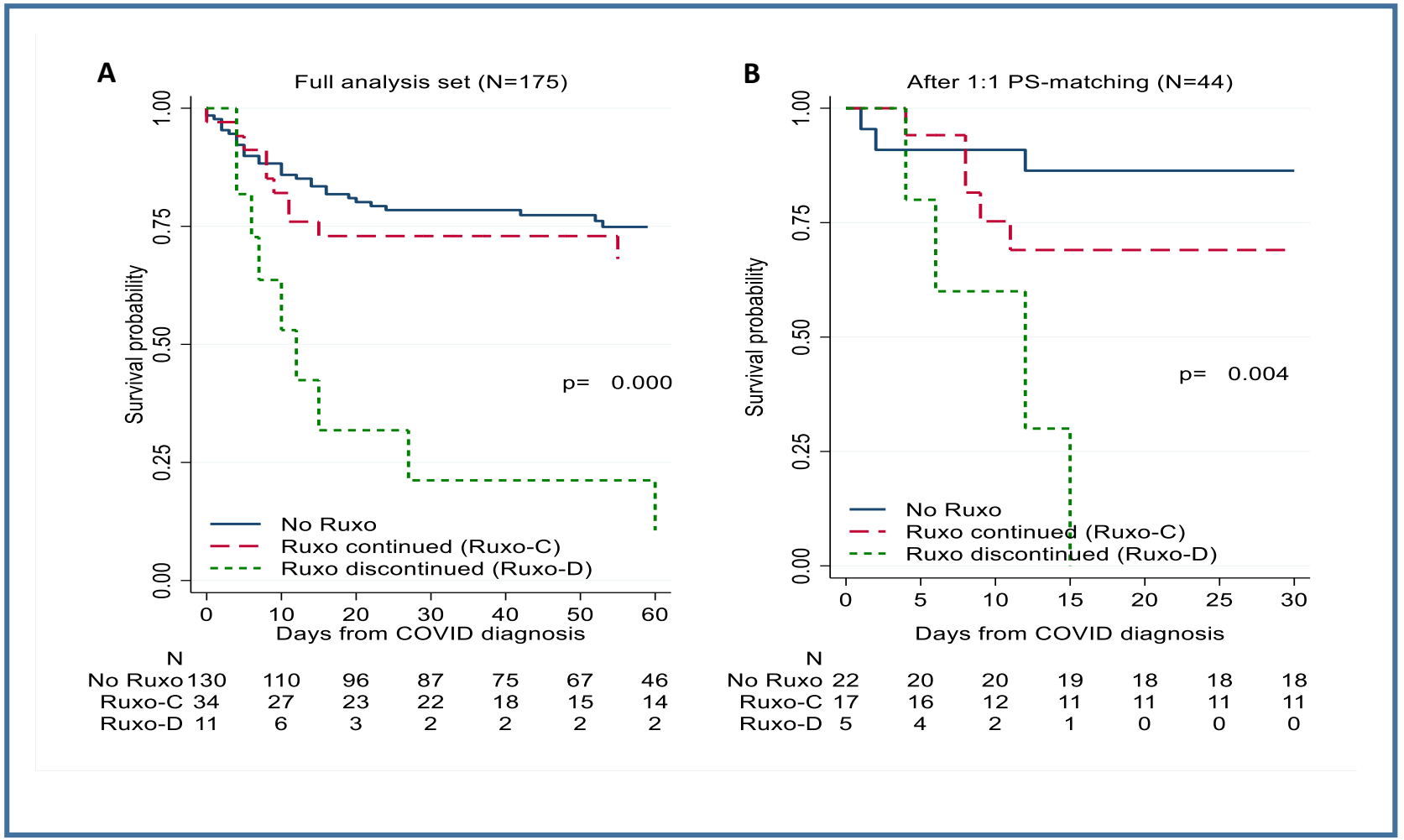
Patients had severe pulmonary disease defined by pulmonary infiltrates on imaging and an oxygen saturation ≤ 93% in air and/or PaO2/FiO2 ratio ≤ 300 mmHg. **Median age was 80.5 years, and 85.3% had ≥ 2 comorbidities.** Median exposure time to ruxolitinib was 13 days, median dose intensity was 20 mg/day. **Overall survival by day 28 was 94.1%.**

Cumulative incidence of clinical improvement in the **full cohort (n=34 pts)** stratified according to the ordinal scale category at baseline (a), and according to the arterial oxygen partial pressure (PaO2)/fraction of inspired oxygen (FiO2) (P/F ratio) at baseline.

Vannucchi et al, Leukemia, 2020

Discontinuation of Ruxo is detrimental during the hyperinflammatory phase of COVID-19.

Full analysis set (A) and propensity score matching (B)



Barbui et al, Leukemia, 2021

Cumulative incidence of thrombosis in ET versus PV/MF.

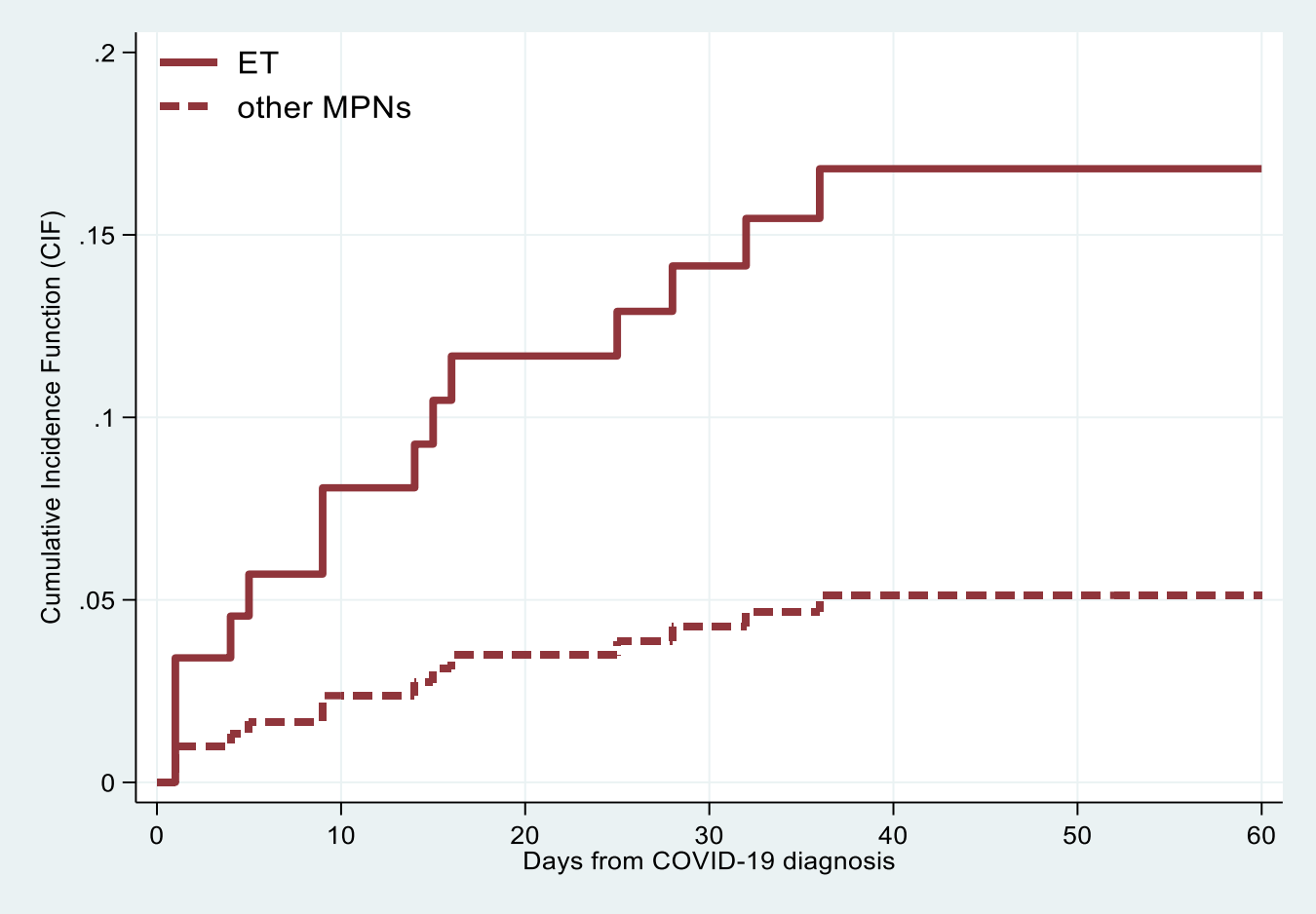
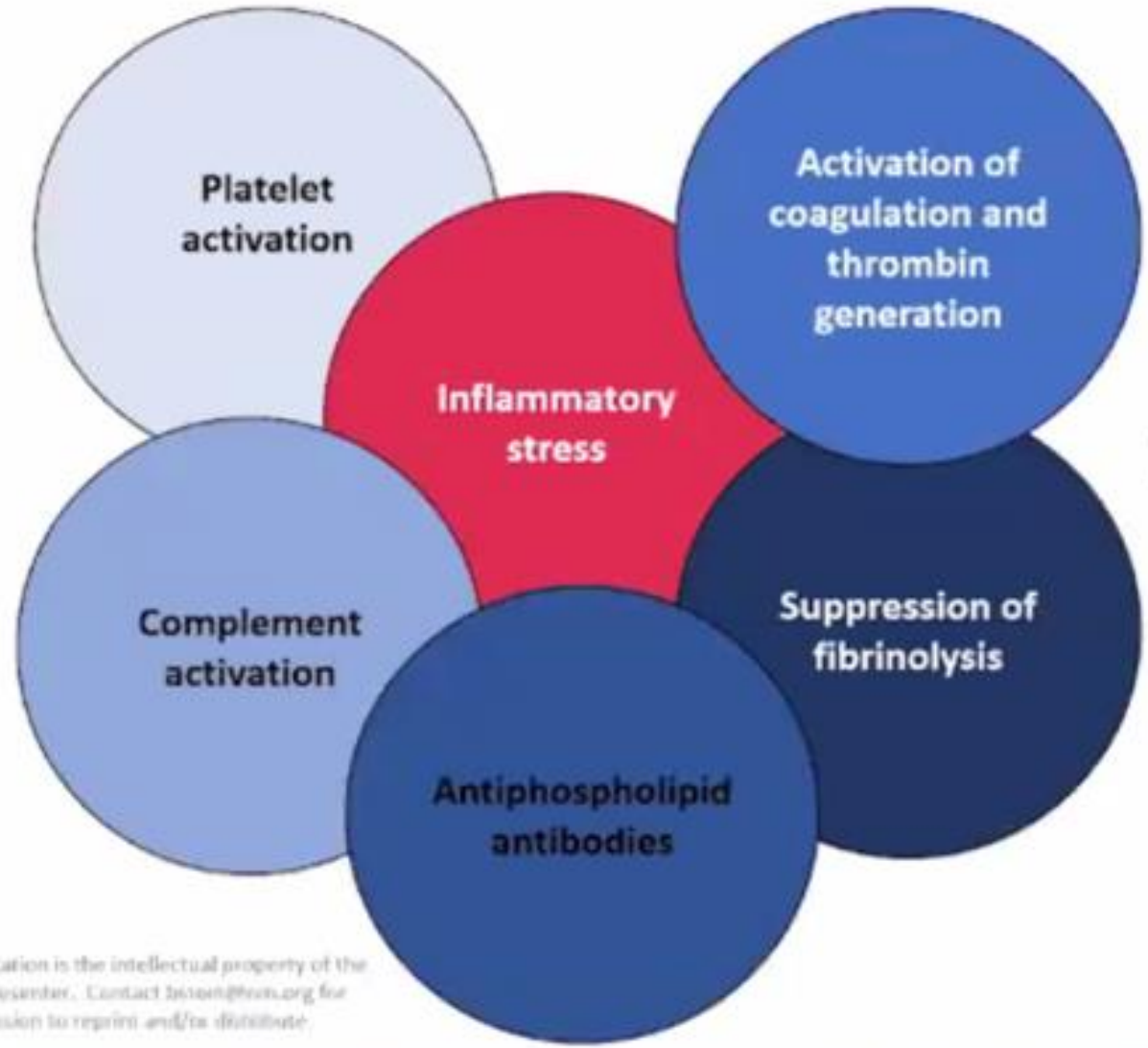


Figure illustrates the remarkable difference in the CIF of thrombosis in patients with ET compared with the other MPN phenotypes.

CIF of arterial/VTE
in ET was 17%
in PV/MF 5%

Of note is the **rapid steepness of the curve starting from the first hours after hospitalization** and reaching the peak after 30 days

COVID19 thrombosis: *"Thromboinflammation"*

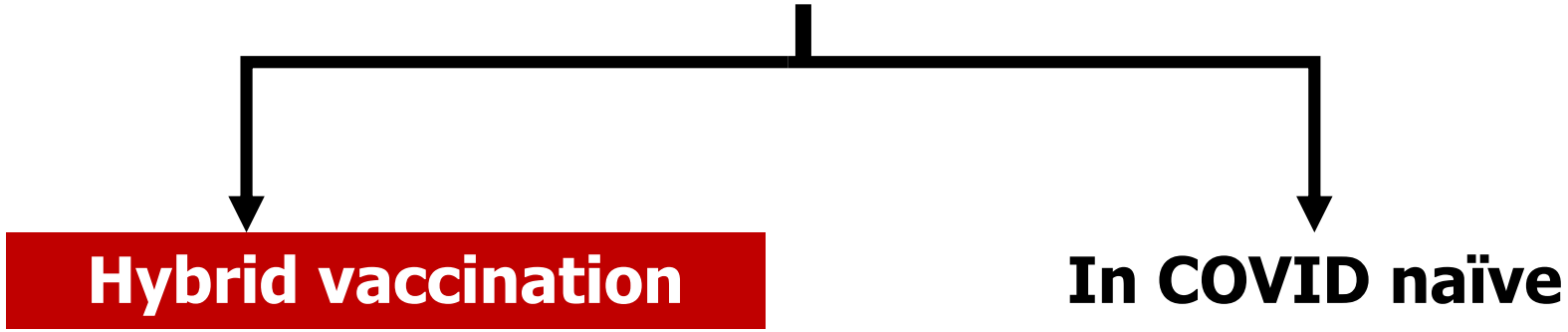


Venous thrombosis
Arterial thrombosis
Microthrombosis
Circuit occlusion

Adapted figure from Iba et al, Critical Care 2020
Connors and Levy, Blood 2020

Vaccination effectiveness versus delta and omicron variants in 518 MPN patients

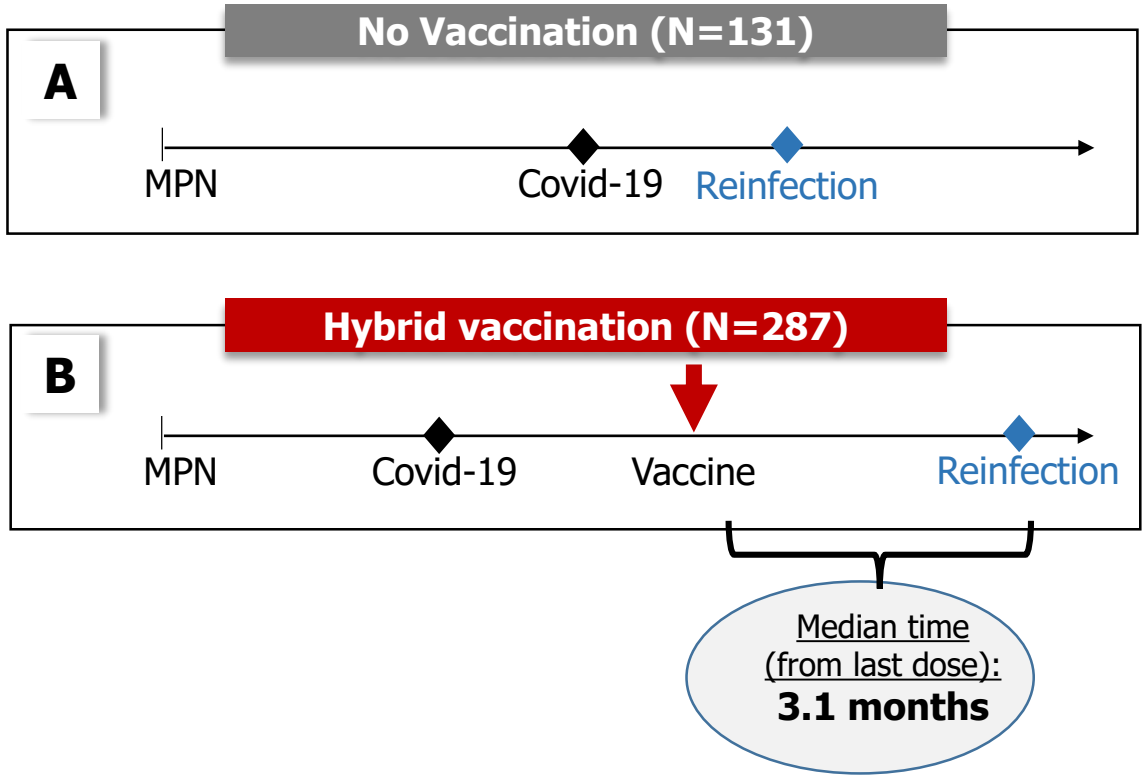
- Vaccination started in Europe in **January 2021**
- Therefore we had the opportunity to assess the **vaccination effectiveness against delta and omicron variants in MPN patients with or without previous Covid-19**



Barbui et al, Blood Cancer J. 2022 Nov 15;12(11):154.

COVID-19 and vaccination

The vaccination campaign began in Europe in early January during the delta VOC



Reinfections N (%)			
8 (6.1%)	p=0.22	OR=1.80 (0.69 - 4.68)
10 (3.5%)		

Characteristics of reinfections

	No vaccination	Hybrid vaccination
	N=8	N=10
Months to reinfection from prior COVID-19	7.5 (4.8-13.1)	14.3 (12.9-16.8)
Wave		
3 (Delta)	3 (37.5%)	1 (10.0%)
4 (omicron)	5 (62.5%)	**9 (90.0%)**
Doses of vaccine		
1/2	-	6 (60.0%)
3/4	-	4 (40.0%)

Barbui et al, Blood Cancer J. 2022 Nov 15;12(11):154.

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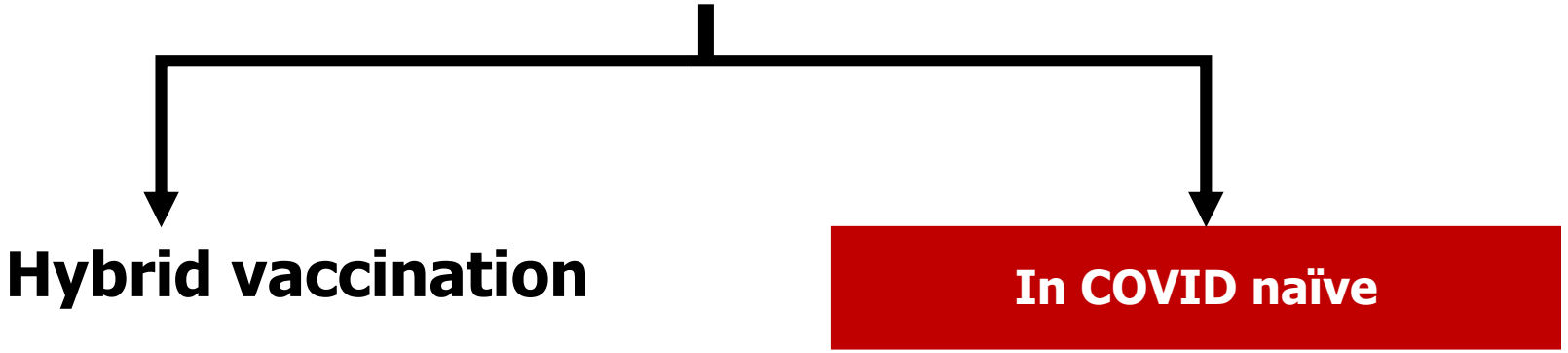
- Vaccination started in Europe in **January 2021**
- Therefore we had the opportunity to assess the **vaccination effectiveness against delta and omicron variants in MPN patients with or without previous Covid-19**



Barbui et al, Blood Cancer J. 2022 Nov 15;12(11):154.

Vaccine breakthrough infections

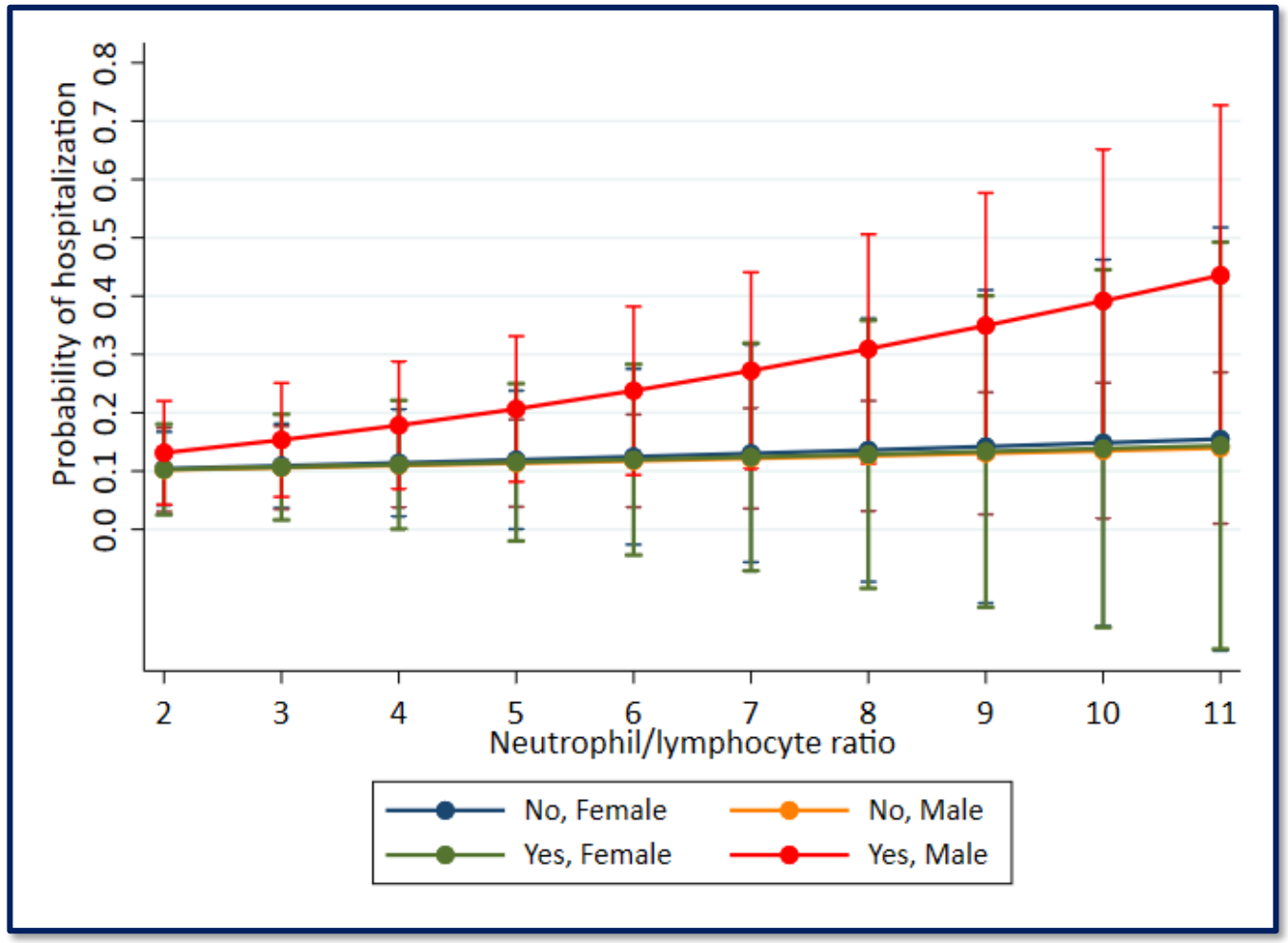
MPN-related characteristics

	Total N=231	Home-treated N=205	Hospitalized N=26 (11%)	p
Male gender	105 (45.5%)	87 (42.4%)	18 (69.2%)	0.010
MPN diagnosis				
ET	89 (38.5%)	80 (39.0%)	9 (34.6%)	0.66
PV	75 (32.5%)	68 (33.2%)	7 (26.9%)	0.52
MF	54 (23.4%)	44 (21.5%)	10 (38.5%)	0.054
ePMF	13 (5.6%)	13 (6.3%)	0 (0.0%)	0.19
MPN treatment pre-covid				
HU	93 (40.3%)	83 (40.5%)	10 (38.5%)	0.84
Anagrelide	19 (8.2%)	19 (9.3%)	0 (0.0%)	0.11
Interferon	5 (2.2%)	5 (2.4%)	0 (0.0%)	0.42
Ruxolitinib	40 (17.3%)	29 (14.1%)	11 (42.3%)	<0.001

Barbui et al, Blood Cancer J. 2022 Nov 15;12(11):154.

Vaccine breakthrough infections: predictors of hospitalizations

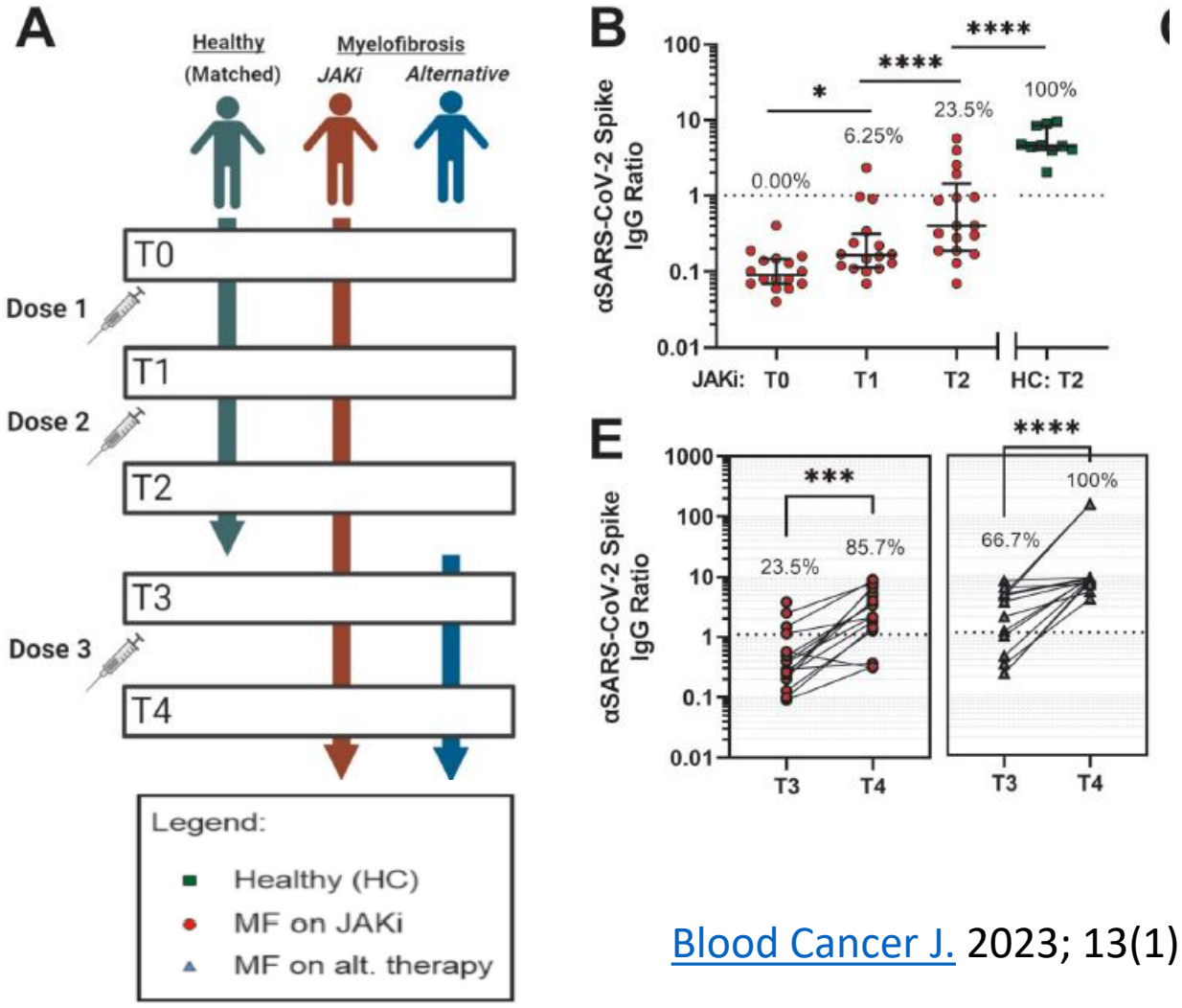
Probability of hospitalization according to ruxolitinib exposure, NLR and gender (multivariate logistic model)



- The increase in the risk of hospitalization **in males treated with ruxolitinib was directly proportional to the inflammatory state** measured with the **neutrophil/lymphocyte ratio.**
- The risk of hospitalization in females (with or without ruxolitinib) was independent from the inflammatory state.

Barbui et al, Blood Cancer J. 2022 Nov 15;12(11):154.
Am J Hematol. 2022

Humoral and cellular immunity to SARS-CoV-2 Ancestral and Omicron BA.5 variants following vaccination in myelofibrosis patients



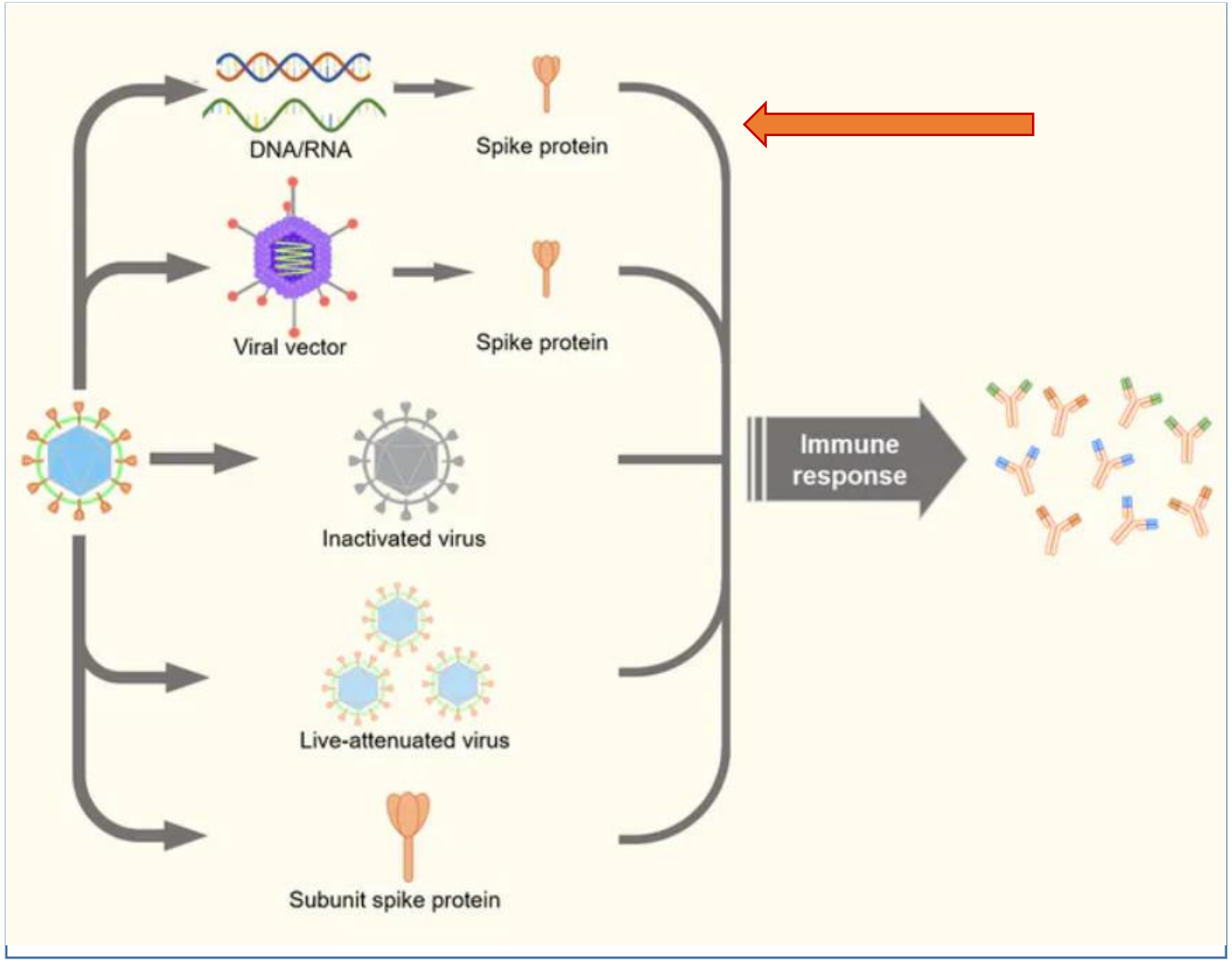
- **Patients with MF should be aware that vaccination might be less effective** so that other measures, such as early institution of anti-viral treatment, may be offered.
- The **lower response especially in those on JAKi therapy,** should be borne in mind by clinicians.
- Promisingly, consistent increases in antibody titer observed for the JAKi cohort with repeated vaccination **suggests further booster dosing may help overcome this impaired response.**

- These results should assist in formulating ongoing **vaccine recommendation guidelines.**

Blood Cancer J. 2023; 13(1): 50.

Considerations on COVID-19 Vaccines

The COVID-19 pandemic has directed worldwide focus towards mRNA-based vaccines.



The foundation for the rapid COVID-19 vaccine development and production was based on years of research exploring mRNA vaccines **as a therapeutic strategy against cancer in preclinical and clinical trials.**

mRNA brings several benefits

1. **mRNA-based vaccines are well tolerated,** easily degraded, and do not integrate into the host genome.
2. mRNA molecules are non-infectious, and mRNA vaccines have the potential to **induce both humoral and cell-mediated immunity**.
3. **the production of mRNA vaccines is fast and inexpensive.**

Cathrine Lund Lorentzen, John B Haanen, Özcan Met, Inge Marie Svane Lancet Oncol October 2022

Cosa ha insegnato la pandemia COVID-19

1. Fragilità dei sistemi sanitari di fronte alla pandemia
2. Come hanno reagito i ricercatori (di base, clinici, industria…)
3. La collaborazione multicentrica particolarmente nelle malattie rare: esempio: il Covid nelle MPN
4. La nuova normalità

Research Letter

ONLINE FIRST

April 6, 2023

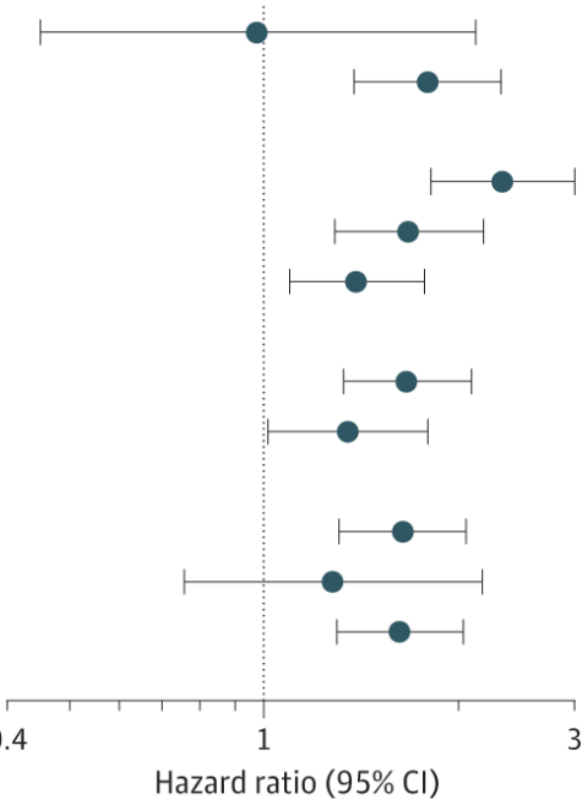
Risk of Death in Patients Hospitalized for COVID-19 vs Seasonal Influenza in Fall-Winter 2022-2023

Yan Xie, PhD[1]; Taeyoung Choi, MPH[1]; Ziyad Al-Aly, MD[1]

≫ Author Affiliations | Article Information

JAMA. Published online April 6, 2023. doi:10.1001/jama.2023.5348

	Death rate at 30 d, % (95% CI)		Excess deaths at 30 d, % (95% CI)	Hazard ratio (95% CI)	*P* value for interaction
	COVID-19	Influenza			
Age, y					
≤65	1.29 (0.77-1.82)	1.33 (0.46-2.20)	-0.04 (-1.06 to 0.98)	0.97 (0.45-2.11)	Reference
>65	6.42 (5.85-6.98)	3.66 (2.77-4.54)	2.76 (1.71 to 3.81)	1.78 (1.37-2.31)	.10
COVID-19 vaccination status					
Unvaccinated	8.75 (7.46-10.01)	3.86 (3.09-4.63)	4.88 (3.39 to 6.37)	2.32 (1.80-3.00)	Reference
1 or 2 doses of vaccine	6.23 (5.22-7.23)	3.79 (3.03-4.56)	2.44 (1.17 to 3.70)	1.66 (1.28-2.17)	.009
Boosted	5.18 (4.55-5.79)	3.77 (3.00-4.53)	1.41 (0.43 to 2.39)	1.38 (1.09-1.76)	<.001
SARS-CoV-2 infection					
Primary infection	6.14 (5.58-6.69)	3.76 (2.99-4.51)	2.38 (1.44 to 3.32)	1.65 (1.32-2.08)	Reference
Reinfection	5.11 (4.11-6.09)	3.85 (3.08-4.62)	1.26 (0.00 to 2.52)	1.34 (1.01-1.78)	.15
Outpatient COVID-19 antiviral treatment					
No	6.03 (5.53-6.53)	3.75 (2.99-4.51)	2.28 (1.37 to 3.19)	1.63 (1.30-2.04)	Reference
Yes	4.81 (2.49-7.07)	3.81 (3.04-4.57)	1.01 (-1.41 to 3.42)	1.27 (0.75-2.16)	.42
Overall	5.97 (5.48-6.46)	3.75 (2.98-4.50)	2.23 (1.32 to 3.13)	1.61 (1.29-2.02)	



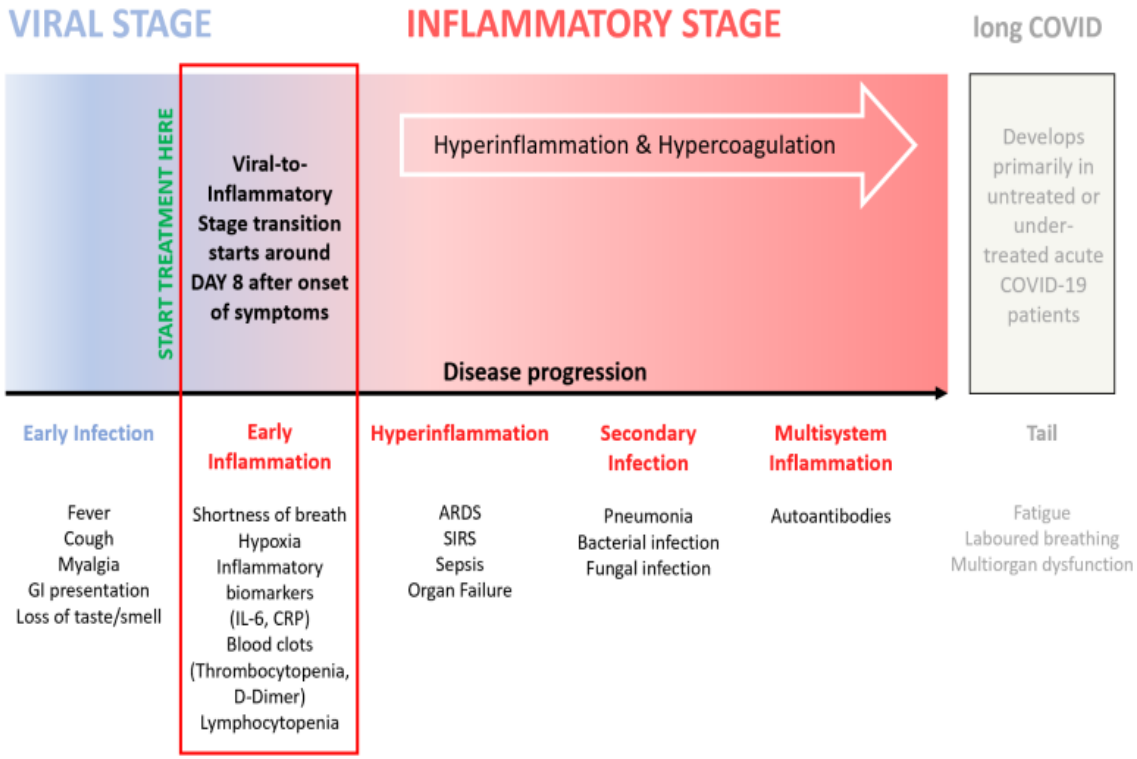
We used the electronic health databases of the US Department of Veterans Affairs (VA). Between October 1, 2022, and January 31, 2023, we enrolled all individuals with at least 1 hospital admission record and an admission diagnosis for COVID-19 or seasonal influenza.

Quali insegnamenti per i pazienti che si ammalano di COVID-19 oggi e che non vengono ricoverati

Nei primi giorni della malattia (malattie live o moderata)

(**i) <u>Anticorpi monoclonali</u>** anti spike che prevengono la penetrazione del virus nelle cellule . Dato che Omicron h molte variant la loro attività è attualmente ridotta.

(**ii) <u>Gli antivirali</u>** Nirmatrelvir-ritonavir, Molnupiravir e remdesivir utilizziamo come target regioni virali conserva e ci si aspetta che possano rimanere attivi anche contro le mutazioni continue di OMICRON



Gandhi RT and Malani PN, JAMA 2022

Gandhi RT, Lynch JB, Del Rio C. Mild or moderate Covid-19. *N Engl J Med*. 2020;383(18):1757-1766.