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CHRONIC MYELOPROLIFERATIVE NEOPLASMS

Second versus first wave of COVID-19 in patients with MPN

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TO THE EDITOR

The first wave of the SARS-CoV-2 coronavirus disease 2019 (COVID-19) began in January 2020, affecting many European countries and leading to an overwhelming of the capacity of acute care hospitals and intensive care units (ICUs). Patients with hematologic malignancies incurring COVID-19 were among the most vulnerable [1–3] and in those with myeloproliferative neoplasms (MPN) including essential thrombocythemia (ET), polycythemia vera (PV), prefibrotic myelofibrosis (pre-PMF) and myelofibrosis (MF), deaths were registered in 28% of cases, being particularly elevated in MF (48%). Age, male gender, admission to ICU, severity of COVID-19 and ruxolitinib discontinuation at COVID-19 diagnosis were independent risk factors for death [4].

The pandemic substantially subsided in Europe until October 2020, likely due to non-pharmaceutical control measures including wearing of a mask, hand washing, social distancing, quarantine and city/region lockdown. These interventions gradually relaxed in consideration of the trade-off between economic sustainability and public health, leading to a second wave of infection, also triggered by new SARS-CoV-2 variants. These raised concerns and uncertainties regarding a possibly new clinical epidemiology of the new virus variants in terms of presentation, severity of acute infection and clinical outcomes.

In the present analysis, we report the outcomes recorded in the 12 months after the first wave declined, pursuing a dual purpose: (i) to describe possible differences of COVID-19 presentation between the two waves and (ii) to evaluate the rate and risk factors of relevant outcomes, including mortality, thrombosis and main clinical events in MPN patients surviving after the acute phase of COVID-19.

The MPN-COVID study is steadily enrolling consecutive adult MPN patients with COVID-19 infection since February 15, 2020. Thirty-nine hematologic centers from Italy, Spain, Germany, France, UK, Poland, and Croatia enrolled 175 and 304 cases in the first and second wave, respectively.

In the present analysis, we report data of the second wave of the pandemic, from July 1, 2020 to June 30, 2021, and compare findings with those obtained during the first wave (i.e., from February 15 to June 30, 2020).

INCIDENCE OF MPN-COVID CASES AND PROBABILITY DENSITY OF DEATH

Supplementary Fig. 1S illustrates the distribution probability of incidence and density of COVID-19 cases by Kernel method [5] for to the two pandemic periods. During the first wave, a peak was documented from April to May followed by a decline during the summer season, whereas the second wave peaked in November/December 2020 and did not completely decline until June 2021. The shape of the incidence curve was substantially similar, while the density function of deaths was less pronounced in the second wave.

PRESENTATION AND THERAPY

In comparison with the first, patients in the second wave were younger, had with less comorbidities and presented with moderate COVID-19 infection (Table 1). They were less symptomatic, most were treated at home, intensive respiratory support being required in a limited number of cases, and an elevation of blood inflammatory markers (C-Reactive Protein and Neutrophil to Lymphocyte Ratio) was found in a lower proportion of cases.

In regard to COVID-19 and MPN directed therapy, steroids were more frequently prescribed than in the first wave ($p = 0.007$); conversely, ruxolitinib was discontinued in fewer MF hospitalized patients. Therefore, all of these clinical and laboratory data were consistent with a less severe COVID-19 infection.

MORTALITY AND RELATED RISK FACTORS

Survival during the first vs. second wave (69% vs. 91%) at 60 days after COVID-19 diagnosis, was statistically different ($p < 0.001$) (Fig. 1A). Among 26 deaths registered during the second wave, 4 (15%) occurred at home, 19 (73%) on the regular word and 3 (12%) in the ICU, and occurred in MF ($n = 17$, 65%), ET ($n = 5$, 19%) and PV ($n = 4$, 15%) ($p < 0.001$). In a multivariate Cox regression model fitted on the whole cohort and adjusted for the wave to which patients belonged (Fig. 1B), significant independent risk factors for death were age over 70 years (HR = 5.22, 95% CI 1.80–15.14, $p = 0.002$), male sex (HR = 1.88, 95% CI 1.13–3.13, $p = 0.016$), severity of COVID-19 defined by the need for respiratory support (HR = 4.45, 95% CI 1.85–10.70, $p = 0.001$), and ruxolitinib discontinuation (HR = 2.98, 95% CI 1.29–6.89, $p = 0.011$). Conversely, continuation of ruxolitinib was not a significant predictor (HR = 1.21, $p = 0.566$).

Compared to the first wave, mortality in patients aged 60–70 was reduced from 35 to 2%. By contrast, deaths in patients over 70 years of age were recorded in 36% and 21% in the first and second wave, respectively. These patients, compared with those <70 years (Supplementary Table 1S), had more comorbidities, prior history of thrombosis, were more frequently hospitalized and in need of respiratory support. In these patients, deaths occurred in 59%, 23% and 18% of MF, ET and PV, respectively. Therefore, the benefit on survival was documented in patients younger than 70 years and more fit, with a limited degree of inflammation.

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Table 1. Patients' characteristics by the two waves of the COVID-19 pandemic.

	First wave N = 175	Second wave N = 304	p value
MPN diagnosis			
ET	51 (29.1%)	110 (36.2%)	0.12
PV	46 (26.3%)	89 (29.3%)	0.48
MF	60 (34.3%)	74 (24.3%)	0.020
pre-PMF	18 (10.3%)	31 (10.2%)	0.98
Treatments at last MPN f-up before Covid-19			
Cytoreduction	141 (80.6%)	233 (77.2%)	0.38
Hydroxyurea	79 (56.0%)	161 (68.8%)	0.092
Anagrelide	8 (5.7%)	10 (4.3%)	0.48
Interferon	4 (2.8%)	7 (3.0%)	0.99
Ruxolitinib	45 (31.9%)	44 (18.8%)	0.002
Other	5 (3.5%)	12 (5.1%)	0.53
ASA	104 (59.4%)	180 (59.4%)	1.00
At Covid-19 diagnosis			
Sex			0.037
Female	73 (41.7%)	158 (52.0%)	
Male	102 (58.3%)	146 (48.0%)	
Age	71.0 (60.0–79.9)	63.3 (54.5–73.8)	<0.001
<60 yrs	42 (24.1%)	117 (38.5%)	
60–70 yrs	37 (21.3%)	83 (27.3%)	
>70 yrs	95 (54.6%)	104 (34.2%)	
Patient disposition			<0.001
Home	40 (22.9%)	208 (68.4%)	
Regular ward	116 (66.3%)	88 (28.9%)	
ICU	19 (10.9%)	8 (2.6%)	
Respiratory supplement need	103 (59.2%)	83 (27.6%)	<0.001
Not invasive	99 (96.1%)	79 (95.2%)	0.75
Invasive	20 (19.4%)	7 (8.5%)	0.037
O_2 saturation %	93.0 (88.0–96.0)	96.0 (90.0–98.0)	<0.001
Symptoms			
Fever	141 (80.6%)	192 (63.2%)	<0.001
Cough	96 (54.9%)	132 (43.4%)	0.016
Dispnea	98 (56.0%)	88 (28.9%)	<0.001
Systemic	36 (20.6%)	30 (9.9%)	0.001
Gastrointestinal	22 (12.6%)	26 (8.6%)	0.16
Comorbidities	130 (74.3%)	192 (63.2%)	0.012
Asthma	3 (1.7%)	8 (2.6%)	0.53
Cerebrovascular	23 (13.2%)	28 (9.2%)	0.18
Kidney impairment	19 (10.9%)	5 (1.7%)	<0.001
Heart disease	25 (14.5%)	25 (8.3%)	0.035
COPD	25 (14.4%)	19 (6.3%)	0.003
Smoke	35 (23.0%)	47 (16.2%)	0.077
Hyperlipidemia	47 (28.0%)	56 (18.5%)	0.018
Obesity	21 (13.1%)	25 (8.3%)	0.098
Reumatic disease	11 (6.4%)	13 (4.3%)	0.32
Hypertension	104 (60.8%)	128 (42.5%)	<0.001
Diabetes	23 (13.4%)	27 (8.9%)	0.13
Chemistry			
Hemoglobin g/dL	12.4 (10.0–13.6)	12.9 (11.1–13.9)	0.019
Hematocrit %	38.4 (32.0–42.4)	39.0 (34.9–43.9)	0.069
WBC x 10^9/L	6.5 (4.6–10.1)	6.8 (5.1–9.8)	0.52
Neutrophils %	75.9 (66.0–83.0)	71.0 (62.5–80.0)	0.053
Lymphocytes %	14.0 (9.0–20.0)	17.6 (10.2–25.0)	0.022
N/L ratio	5.4 (3.4–8.9)	4.1 (2.6–8.4)	0.038
Platelets x 10^9/L	252.0 (152.0–394.0)	350.0 (224.0–456.0)	<0.001
LDH U/L	426.0 (264.5–641.5)	356.0 (229.0–622.0)	0.15
CRP mg/L	74.0 (26.0–156.8)	51.5 (10.3–100.0)	0.008
D-dimer ng/ml	801.0 (398.0–1655.0)	924.5 (480.0–2340.0)	0.20
Covid-directed treatments			
Steroids	45 (27.8%)	121 (40.3%)	0.007
Antibiotics	114 (70.4%)	123 (41.0%)	<0.001
Hydroxychloroquine	100 (60.2%)	9 (3.0%)	<0.001
Antivirals	57 (34.3%)	19 (6.4%)	<0.001
Experimentals	19 (11.2%)	12 (4.0%)	0.002
Antithrombotics	93 (56.0%)	114 (38.4%)	<0.001
MPN-directed treatment change			
Hydroxyurea discontinuation	9 (11.3%)	11 (6.6%)	0.21
Anagrelide discontinuation	1 (12.5%)	2 (20.0%)	0.67
Interferon discontinuation	1 (25.0%)	1 (14.3%)	0.66
Ruxolitinib discontinuation	11 (23.9%)	4 (8.7%)	0.048
Outcomes of the acute phase			
Death	50 (28.6%)	26 (8.6%)	<0.001
Time to death (days)	9.5 (4–16)	11.0 (6–20)	0.673
Thrombosis	14 (8.0%)	5 (1.6%)	0.001
Time to thrombosis (days)	11.5 (4.0–25.0)	1.0 (1.0–6.0)	0.52
Arterial	3 (1.7%)	1 (0.3%)	0.141
Venous	12 (6.9%)	4 (1.3%)	0.002

Continuous variables are summarized by median (interquartile range [IQR]).

THROMBOSIS

At 60 days from COVID-19 diagnosis, only 5 incident cases of thrombosis were registered out of 304 patients (1.6%) during the second wave, significantly lower than in the first wave (14 thrombosis on 175 patients, 8.0%), although an antithrombotic treatment was prescribed less frequently (Table 1). Such findings mirror the less severe clinical presentation noticed in the present case series. However, almost all events ($n = 4/5$) were venous and we confirmed in multivariate model that most of these events occurred in patients with ET (SHR = 4.4, 95% CI 1.8–10.7, $p = 0.001$). As in the first wave, we did not find a significant difference in venous thrombosis between cases treated with prophylactic doses of heparin compared to controls.

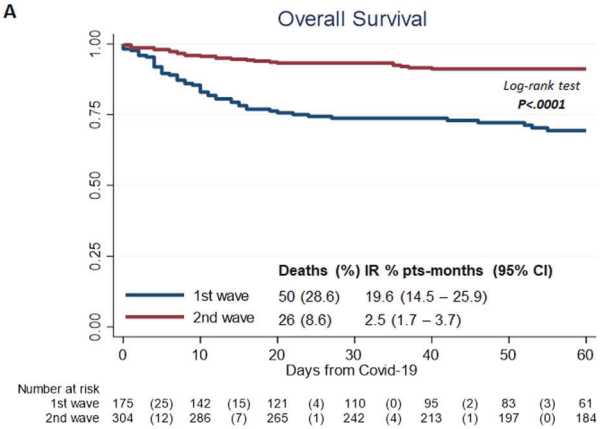
EVENTS IN PATIENTS SURVIVING AFTER THE ACUTE PHASE

Two-hundred twenty-three patients survived after the acute phase of the second wave of COVID-19 and were followed up for a median of 141 days (IQR: 94–173). Two of them died, 4 were diagnosed with deep vein thrombosis of the legs with or without pulmonary embolism and one with arterial cerebral thrombosis, and 4 developed bleeding, accounting together for an event-free survival (EFS) of 93.82%, a figure significantly different from the first wave (EFS: 65.70%, $p = 0.0312$).

COMMENT

This is the largest analysis of MPN patients who contracted COVID-19 in the 12 months subsequent to the first wave of the coronavirus pandemic, which was characterized by conditions of exceptional lethality. Patients of the second wave presented, compared to those of the first, with a less severe disease, including a lower degree of inflammation, leading to hospitalization in a

A



B

Covariate	Haz. Ratio	P-value
2nd wave (vs. 1st wave)	**.57 (0.33-0.97)**	**0.037**
Male sex (vs. female)	**1.88 (1.13-3.13)**	**0.016**
Comorbidities (at least one)	1.19 (0.61-2.31)	0.615
Age at Covid-19		
<60 yrs	1 (ref)	
60-70 yrs	2.44 (0.78-7.65)	0.126
>70 yrs	**5.22 (1.80-15.14)**	**0.002**
MPN diagnosis		
ET	1 (ref)	
PV	.68 (0.32-1.44)	0.311
MF	1.64 (0.85-3.16)	0.140
pre-PMF	.49 (0.16-1.49)	0.207
Patient disposition		
Home	1 (ref)	
Regular ward	1.71 (0.58-5.03)	0.331
ICU	3.30 (0.96-11.33)	0.058
Need of respiratory support	**4.45 (1.85-10.70)**	**0.001**
Ruxolitinib administration	1.21 (0.63-2.34)	0.566
Ruxolitinib discontinuation	**2.98 (1.29-6.89)**	**0.011**

Fig. 1 Overall survival by waves of coronavirus pandemic. Kaplan-Meier curves of overall survival by the two waves of Covid-19 (**A**) and multivariate Cox proportional hazard model for mortality during the acute phase (**B**).

smaller percentage of cases. Overall, the mortality rate was significantly lower, likely due to early COVID-19 diagnosis, facilitated by the greater availability of swabs than in the first wave, more efficient management of infected patients, better prepared health systems and preferential protection of older and higher-risk MPN vulnerable subjects. However, patients over 70 years still presented with an excess of mortality, particularly when associated with comorbidities and an MF phenotype. Unfortunately, no data are available so far in our series to support a role of vaccinations. The high thrombosis rate in patients with ET was confirmed, suggesting that in this MPN phenotype regimens of antithrombotic prophylaxis in addition to heparin should be explored. Also in the second wave, but to a lesser extent than in the first, the health consequences of COVID-19 protracted far beyond acute infection, suggesting careful and permanent surveillance of patients with MPN who have survived the acute phase of SARS-CoV-2 virus infection.

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AUTHOR CONTRIBUTIONS

TB conceived and designed the study, supervised the analysis and wrote the paper. AMV, VDS, AR revised the study and contributed to manuscript writing. AM directed the project. AC planned and performed statistical analyses. AG, GC contributed to dataset preparation. AI, MAS, EME, ER, FL, MM, RD, MGK, BC, MLF, MMAC, FP, PG, GB, CH, MAF, MB, AAL, JJK, EBC, AP, KSQC, MG, VGG, AMS, EMM, MR, JCHB, SO, GCT, MSS, RK, BNE, AA, BXC, ELA, SK, DC, CB, EC, AKdN, FC, OB, SB, LB, MB, NCG, collected data. All authors revised and approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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