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CORRESPONDENCE

Determinants of early triage for hospitalization in myeloproliferative neoplasm (MPN) patients with COVID-19

To the Editor:

In the clinical course of COVID-19, the disease is primarily driven by the replication of SARS-CoV-2 and subsequently includes a dysregulated inflammatory response to the virus leading to tissue damage, thrombosis, and other life-threatening complications. In chronic myeloproliferative neoplasms (MPN) including essential thrombocythemia (ET), polycythemia vera (PV), prefibrotic myelofibrosis (pre-PMF), and overt myelofibrosis (MF) an excess of deaths was seen during the first wave, particularly in MF.[1] The pandemic original wave, sustained by the wild type virus, substantially subsided in Europe until October 2020 but new viral variants of concern (VOCs) emerged thereafter, raising new difficulties of management of these vulnerable unvaccinated patients. Emergency departments were overwhelmed by the epidemic and confronted both with highly suspected SARS-CoV-2 infection patients and with early or advanced documented disease. This made difficult to assess factors associated with a rapid progression into a life-threatening severe disease particularly in patients with MPN, many of whom were in need of cytoreductive or antithrombotic therapy.

With the aim to investigate determinants of hospitalization and severity of COVID-19 and to explore whether MPN patients could have specific risks of critical illness, we examined a large cohort of 479 patients with MPN diagnosed in several European countries during the first and second wave of the pandemic. Patients were reported in the MPN-COVID study (ClinicalTrials.gov identifier: NCT04385160), promoted by European LeukemiaNet (ELN) and included consecutive WHO-2016 diagnosed MPN patients who contracted SARS-Cov-2 infection since February 15, 2020, across Europe by 39 participating centers. Details of protocol design and operational procedures have already been reported.[1,2] Waves of the COVID-19 pandemic were divided into two periods, according to the type of predominant circulating VOCs in Europe. The first wave, corresponding to wild type variant, covered the period from February 15 to June 30, 2020; the second wave, started from July 1, 2020 to June 30, 2021 included the alpha, beta, and gamma VOCs infection. Statistical analysis was carried out at the biostatistical laboratory of the Foundation for Research (FROM) at Papa Giovanni XXIII Hospital in Bergamo.

Continuous variables were summarized with median along with interquartile range (IQR), and categorical ones were presented as frequencies and percentages. Characteristics of the study population were stratified for hospitalization and differences between the two groups tested with the χ^2 test (or Fisher's exact test where appropriate) or rank-sum test for categorical or continuous variables, respectively. Frequency distributions and Kernel density functions were calculated for COVID-19 incidence across time by patient's disposition. Receiver Operating Characteristic (ROC) curves for the prediction of hospitalization were used to compare different blood count measures and the Liu's method to find the best cut-off. A logistic Generalized Additive Model (GAM) was fitted to test parameters continuous trend prediction for the risk of hospitalization.

Using a multivariable logistic regression model, association with hospitalization was evaluated for the following variables: age, sex, presence of at least one comorbidity, MPN type, previous thrombosis, ruxolitinib exposure, COVID-19 main symptoms (fever, dyspnea, systemic), O_2 saturation, and neutrophils-to-lymphocytes ratio (NLR). Onset of dyspnea was ascertained by the physician and often associated with cough and precipitous drops in oxygen saturation. Marginal prediction probabilities of hospitalization were calculated in a final logistic model that included statistically significant factors only and their terms of interaction.

COHORT CHARACTERISTICS AND UNIVARIATE ANALYSIS

The enrolled and analyzed patients encompassed ET ($n = 175$), PV ($n = 158$), MF ($n = 91$), and pre-PMF ($n = 55$). Based on each individual single center physician's decision, 248 and 231 were managed at home or hospitalized, respectively. Note in the Figure S1 the difference in the frequency and density of hospitalization in the first wave compared to the following one up to June 2021.

Differences between non-hospitalized and hospitalized patients are summarized in Table S1. Compared to outpatients, those admitted to hospital were more likely to be men (58.9% vs. 45.2%, $p = .003$), older than 70 years (61.3% vs. 29.0%, $p < .001$), with at least one comorbidity (79.7% vs. 55.5%, $p < .001$), and history of thrombosis (26.5% vs. 16.6%, $p = .008$). MF cases were more frequently hospitalized rather than PV, ET, or pre-PMF (38.5% vs. 18.1%, $p < .001$) as well as the proportion of patients on ruxolitinib was higher in hospital than at home (25.7% vs. 12.1%, $p < .001$).

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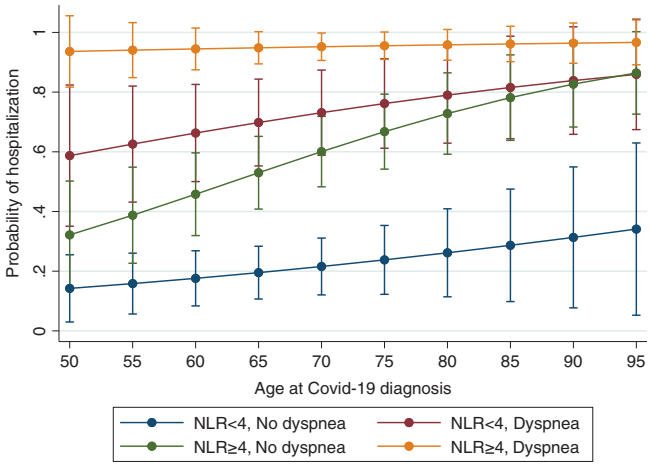

FIGURE 1 Marginal probability of hospitalization according to age, NLR and dyspnea. *NLR*, *neutrophil-to-lymphocyte ratio*. Marginal probability of hospitalization across different patient's ages calculated from the logistic model that included age, NLR and dyspnea and their terms of interaction.

Other differences between the two groups concerned the greater frequency in hospitalized patients of lower values of hemoglobin (12.1 vs. 13.3 g/dL, $p < .001$), platelet number (250 vs. 390 $\times$ 10^9/L, $p < .001$), absolute lymphocyte count (0.8 vs. 1.4 $\times$ 10^9/L, $p < .001$) and higher neutrophil counts (5.1 vs. 4.5 $\times$ 10^9/L, $p = 0.022$), leading to a significant higher levels of NLR inflammatory biomarker (6.6 vs. 3.2, $p < .001$).

Among blood count measures, the best sensitivity and specificity values predicting for hospitalization were found for NLR, particularly compared with lymphopenia alone (Figure S2a): AUC was 77.28% by ROC analysis, with the optimal cut-off of 4, and log transformed Odds Ratios (logORs) for hospitalization by GAM logistic regression analysis was almost linear (Figure S2b).

PREDICTORS OF HOSPITALIZATION

In multivariate analysis, adjusting for sex, comorbidity, fever, systemic symptoms, O_2 saturation, previous thrombosis, MPN type, and ruxolitinib exposure, three factors emerged as independent predictors of hospitalization: age over 70 years, (OR = 2.91, $p = .037$), dyspnea (OR = 7.13, $p < .001$) and NLR ≥4, (OR = 7.04, $p < .001$).

Of note, percentages of patients with these factors (i.e., age ≥ 70, dyspnea, NLR ≥4) in the first original wave (February–June 2020) was 55%, 56%, and 66%, respectively; while in the subsequent waves (until June 2021), the same frequencies declined substantially ($p < .001$), albeit to a lesser extent for NLR ($p = .015$) (Figure S3). Nevertheless, the same three factors had a similar frequency during the first and second wave analyzed separately in outpatients and in the hospitalized ones. The only exception was for dyspnea, present in a lower percentage of outpatients in the second than in first wave.

The marginal effect of NLR and dyspnea was evaluated across different age classes in a model fitted to test the interaction terms of the three significant variables (Figure 1). In younger patients (i.e., from 50 to 70 years) dyspnea was the stronger predictor than increased NLR; conversely, dyspnea and NLR both showed a high and comparable marginal effect in age > 80 years. Remarkably, the probability of hospitalization consistently exceeded 90% for any age group when dyspnea and NLR were concomitantly present, and their combination was more prevalent in MF (42%) than in the other diseases (24%, 25%, and 29% in pre-PMF, PV and ET patients, respectively). In addition to predict hospitalization, dyspnea and NLR≥4 were also associated with severity of COVID-19 illness, based on the need of respiratory support (OR = 2.44, $p = .023$).

Our results indicate that in patients with MPN at COVID-19 diagnosis, the concomitant presence of dyspnea and elevated NLR inflammatory biomarker identified a subgroup of patients at a higher risk for hospitalization. Moreover, we showed that the onset of early dyspnea was also a factor to predict the worsening of respiratory function in these hospitalized patients.

In non MPN population, age and comorbidities were found powerful predictors of requirement for admission to hospital rather than outpatient care; however, degree of oxygen impairment and markers of inflammation were most strongly associated with poor outcomes during hospital admission. Accordingly, it was suggested that clinicians should consider routinely obtaining inflammatory markers during hospital stay for people with COVID-19.[3] We highlight here that inflammatory biomarkers should be determined at the very beginning onset of coronavirus infection just after the diagnosis of COVID-19 since these MPN could benefit of a prompt therapy.

Notably, the combination of dyspnea and elevated NLR levels was prevalent in MF patients rather than in PV, ET, or pre-PMF and had an independent prognostic value at any age. This is not surprising given that among the classic MPNs, a systemic and latent inflammatory status is intrinsically more pronounced in MF than in other MPNs and the SARS-CoV-19 may exacerbate the deleterious clinical effect consequent to hyperinflammation status.[4] It follows that the presence of elevated levels of NLR as a consequence of the marked reduction of lymphocyte counts and neutrophilia, should be considered a warning signal for a prompt therapy-decision making with anti-inflammatory and anti-viral therapy, particularly in the presence of symptoms. Non-steroidal-anti-inflammatory-drugs (NSAIDs) have been recently suggested for the management of outpatients with early symptoms of COVID-19[5] to mitigate hospitalization and infection severity. However, whether NSAIDs can provide a favorable risk–benefit profile in all MPN patients has not yet been explored and caution should be exerted in MPN patients who are constitutively prone to bleeding tendency.

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CONFLICT OF INTEREST

None of the authors have any conflicts of interest or financial ties to disclose in connection with the current paper.

DATA AVAILABILITY STATEMENT

Aggregated data available by request. Patient-level data will not be shared

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REFERENCES

1. Barbui T, Vannucchi AM, Alvarez-Larran A, et al. High mortality rate in COVID-19 patients with myeloproliferative neoplasms after abrupt withdrawal of ruxolitinib. *Leukemia*. 2021;35(2):485-493.
2. Barbui T, Iurlo A, Masciulli A, et al. Second versus first wave of COVID-19 in patients with MPN. *Leukemia*. 2022;36(3):897-900.
3. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in new York City: prospective cohort study. *BMJ*. 2020;369:m1966.
4. Tefferi A, Vaidya R, Caramazza D, Finke C, Lasho T, Pardanani A. Circulating interleukin (IL)-8, IL-2R, IL-12, and IL-15 levels are independently prognostic in primary myelofibrosis: a comprehensive cytokine profiling study. *J Clin Oncol*. 2011;29(10):1356-1363.
5. Perico N, Cortinovis M, Suter F, Remuzzi G. Home as the new frontier for the treatment of COVID-19: the case for anti-inflammatory agents. *Lancet Infect Dis*. 2022;(22):433-439. doi:10.1016/S1473-3099(22)00433-9

SUPPORTING INFORMATION

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