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Severity of SARS-CoV-2 infection in myelofibrosis patients treated with ruxolitinib: Observational, prospective, of the case-control type study

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Abstract

The aim of the present study is to investigate the course and outcome of the disease in MF patients infected with SARS-CoV-2 with special attention to patients on ruxolitinib therapy.

The study is observational, prospective, conducted in real life settings, of the case-control type. SARS-CoV-2 were followed as an active group, and MF patients who were not infected as a control group. The subject of the study are patients with MF treated with ruxolitinib during the period 03.2020. until 03.2022. Sources of data for the studied indicators are the patients, their health files, or their relatives. To estimate the risk of adverse outcomes in COVID 19 disease in patients with MF and fatal outcome, a number of risks were calculated.

Of the monitored patients with MF, a total of 5 (14.3%) died during this period. Of these, 3 patients died as a result of progression of the haematological disease or a complication of another concomitant disease. 2 (12.5%) patients died from COVID 19 infection or its complications. Both had a severe infection. A thrombotic event was reported in 1 patient. During this period, 9 (25.7%) of the monitored patients were vaccinated. The treatment was stopped due to COVID 19 in 4 of the sick patients. In the rest, it was continued without a change in the dose.

Disease progression is a more important factor, as the chance of death after progression is 33% more likely than after COVID 19. Among MF patients, the probability of getting COVOD 19 is 45%, but the results show that they will successfully recover from it (30% higher probability).

Patients with MF have COVID 19 more often than the general population. Mortality in the observation group was higher compared to the general population but comparable to published data for patients with MF. The disease is more often mild or medium-severe.

Keywords: COVID 19; Myeloproliferative neoplasms; Myelofibrosis; Treatment

1. Introduction

SARS-CoV-2 coronavirus infection appeared in the world in December 2019 [1]. The disease it causes was named COVID 19, and in January 2020 the World Health Organization (WHO) declared COVID 19 a pandemic [2]. The first cases of COVID 19 in Bulgaria were registered at the beginning of March 2020 [3]. The disease can proceed as a respiratory infection with the possibility of severe respiratory distress syndrome and is characterized by an increased risk of thrombosis [4].

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Numerous studies indicate evidence of a more severe course of infection in patients with chronic diseases, but data on the evolution of COVID 19 in patients with rare haematological diseases are limited [5]. On the one hand, a different manifestation may be expected due to immune suppression associated with the disease and/or the treatment of the disease. Myeloproliferative neoplasia's (MPNs) are a heterogeneous group of diseases. Patients with polycythaemia vera (PV) and essential thrombocythemia (ET) are not at increased risk of developing infections but are at increased risk of thrombosis and bleeding [6]. Patients with myelofibrosis (MF) may be at increased risk of infection especially in advanced disease, with infections accounting for 11% of the causes of death in patients with MF [7]. Studies on the impact of SARS-CoV-2 infection on the course and the outcome of the disease in patients with MF are limited worldwide and are not available in Bulgaria, which is why we focused our interest in this area.

The aim of the present study is to investigate the course and outcome of the disease in MF patients infected with SARS-CoV-2 with special attention to patients on ruxolitinib therapy.

Main scientific questions of the study are:

- What is the frequency of COVID 19 in patients with MF (Primary myelofibrosis (PMF), post-Polycythaemia vera (post-PV) MF, post-Essential thrombocythemia (post-ET) MF) treated with ruxolitinib, the severity of the course of the disease; the incidence of thrombotic events and mortality?
- Does the therapy of haematological disease change because of COVID 19?

2. Material and methods

2.1. Design of the study

The study is observational, prospective, conducted in real life settings, of the case-control type. SARS-CoV-2 were followed as an active group, and MF patients who were not infected as a control group. The subject of the study are patients with MF treated with ruxolitinib during the period 03.2020. until 03.2022 in the Specialized Hospital for Active Treatment of Haematological Diseases in Sofia. During the indicated period, 35 patients with MF were treated at the hospital, all of whom were on ruxolitinib therapy at the beginning of the follow-up.

Sources of data for the studied indicators are the patients, their health files, or their relatives.

Data on the presence or recurrence of COVID 19 were collected from the patients themselves during a visit to the hospital or by telephone. Data on the severity of the COVID 19 course were also evaluated by patient information on a three-level scale (asymptomatic or mild; moderate-severe and severe course), as well as data on the presence or absence of a vaccine and the type of vaccine.

The change in therapy is based on information from the attending physician and from the patients' health records. Information on the presence of thrombotic events was extracted from health records, and information on deaths from relatives of the deceased.

Ethical committee of the hospital approved the study.

2.2. Risk analysis

To estimate the risk of adverse outcomes in COVID 19 disease in patients with MF and fatal outcome, a number of risks were calculated. The first group of risks is when meeting the infection for the development of a disease and the second group for a disease for a death. Probabilities as p2 and p1 were calculated as percentage ratios of the number of patients from the general group and the number of patients from the respective groups. Based on these, the risk differences, relative risk, relative risk reduction and odds ratio were calculated.

$$\text{Risk difference (RD)} = p2\text{-}p1\ (\%)$$

$$\text{The relative risk (RR)} = p1/p2$$

$$\text{Relative Risk Reduction (RRR)} = 1\text{-}RR\ (\%)$$

Odds ratio (OR) = r1(n2-r2)/r2(n1-r1); where r1 and r2 are the cases in each group, n1 and n2 is the number observed in the group.

Calculations were performed following the recommendations of the Evidence-Based Medicine Group [8].

3. Results

3.1. Characteristics of the patients

Of the monitored patients with MF, a total of 5 (14.3%) died during this period. Of these, 3 patients died as a result of progression of the haematological disease or a complication of another concomitant disease. 2 (12.5%) patients died from COVID 19 infection or its complications. Both had a severe infection. One of the patients has a co-morbidity of severe chronic obstructive pulmonary disease (COPD) with frequent exacerbations; the second patient was free of comorbidities in a stable haematological disease state. He died of thrombosis (pulmonary thromboembolism). A thrombotic event was reported in 1 patient.

During this period, 9 (25.7%) of the monitored patients were vaccinated. All were given an mRNA vaccine. Of these, after vaccination, 1 patient had proven COVID 19 infection during this period. The disease had a mild course.

All patients with MF, diagnosed COVID 19 were distributed according to the severity of the disease as follows on Figure 1.

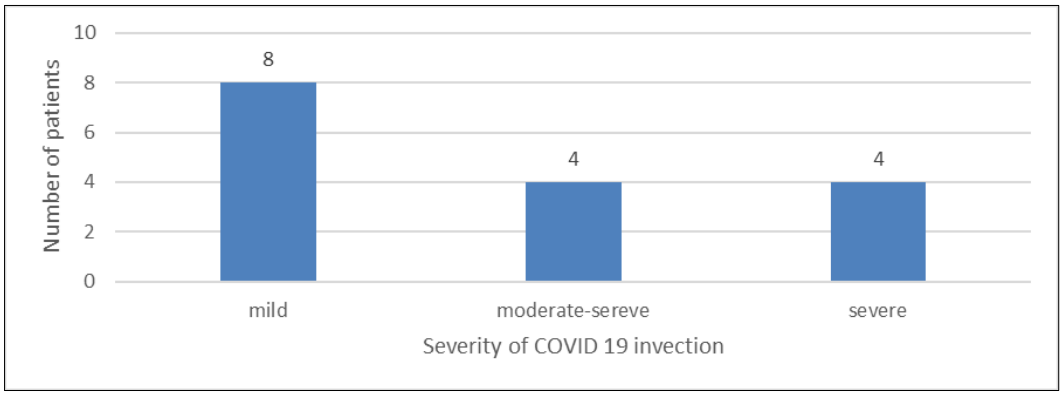

Figure 1 Distribution of infected patients according to severity of COVID 19 infection

Patients who were not diagnosed with COVID 19 (n=19) were on the following daily dose of ruxolitinib – 5 at 10mg/day; 5 at 20mg/day; 5 at 30mg/day; 4 at 40mg/day.

Patients who were diagnosed with COVID 19 infection were distributed as follows according to the severity of the course and the daily dose of the drug (Figure 2): with a mild course - 1 per 10mg/day; 3 at 30mg/day; 4 at 40mg/day; with moderate-severe course – 1 per 10mg/day; 2 at 30mg/day; 3 at 40mg/day; with severe course - 2 at 30mg/day; 2 at 40mg/day.

The treatment was stopped due to COVID 19 in 4 of the sick patients. In the rest, it was continued without a change in the dose.

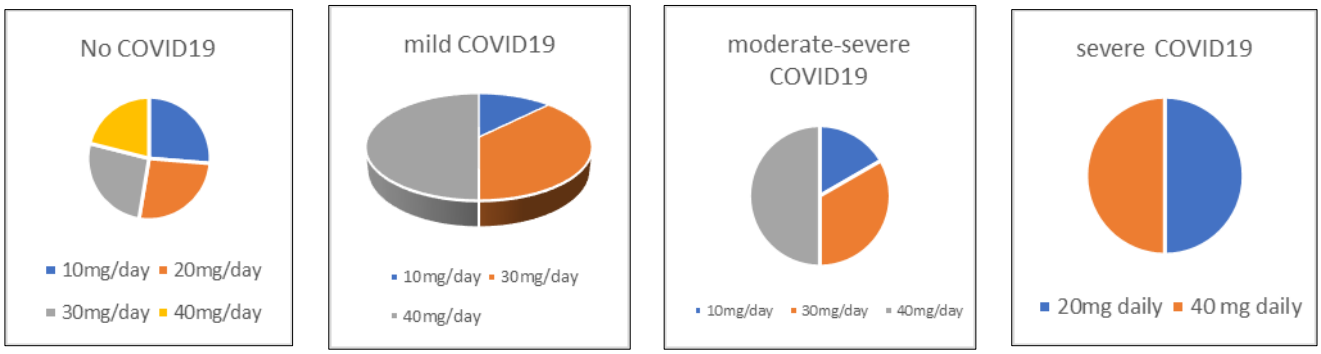

Figure 2 Distribution of patients according to ruxolitinib dosage and severity of COVID 19

3.2. Results of the risk analysis

Table 1 presents the estimated risks of disease from Covid-19 in patients with MF, and Table 2 presents the risk of death in patients with MF and Covid-19.

Table 1 Risks for having COVID 19 in MF patients

Indicator	Value
Total number of patients with MF	35
MF patient without COVID 19 (r2)	19
MF patient with COVID 19 (r1)	16
% of patients with MF and COVID 19 (p1)	45.7
% of patients without MF and COVID 19 (p2)	54.3
Risk difference RD (p2-p1)	8.60 %
95% confidence interval (CI) for RD	-14.769 – 31.912
Relative risk – RR (p1/p2)	0.842
95% CI for RR	0.525 - 1.35
Relative risk reduction – RRR (1-RR)	15.8
Odds ratio (OR) = r1(n2-r2)/r2(n1-r1)	0.709
95% CI for OR	0.277 – 1.816

Table 2 Risks for death for MF patients with COVID 19

Indicator	Value
MF patient with COVID 19 (n1)	16
MF patient without COVID 19 (n2)	19
Deceased in group n1	2
Deceased in group n2	3
% deceased in group n1 (p1)	12.5
% deceased in group n2 (p2)	15.8
Risk difference (RD) (p2-p1)	3.30%
95% CI for RD	-19.764 – 26.343
Relative risk – RR (p1/p2)	0.792
95% CI for RR	0.15 - 4.168
Relative risk reduction – RRR (1-RR)	20.8
Odds ratio (OR) = r1(n2-r2)/r2(n1-r1)	0.762
95% CI for OR	0.111 – 5.237

Deaths in patients without COVID 19 were more than in patients with COVID 19. An odds and risk assessment showed that in this cohort of patients, COVID 19 did not significantly alter the probability of death. Disease progression is a more important factor, as the chance of death after progression is 33% more likely than after COVID 19.

Due to the low number of patients in both groups, the confidence interval varies between 0.1 and 5, indicating the uncertainty of the estimate. Among MF patients, the probability of getting COVOD19 is 45%, but the results show that they will successfully recover from it (30% higher probability).

It could be assumed that disease progression is a greater risk factor than contracting COVID 19.

4. Discussion

This is the first study in Bulgaria that investigates the risk and severity of SARS-CoV-2 infection in patients with MF. According to the data on the country's population and the number of people infected with COVID 19 at the end of September 2022 the average incidence of disease is about 25% [9, 10]. According to the same data, the share of deaths from COVID 19 for the same period is 3%. Our observed mortality in the MF population was 12.5%, which is higher than the national average but comparable [9].

25.7% of patients were vaccinated, which corresponds to the vaccination density in the country according to Union Electronic Portal data [9]. According to international recommendations, there are no contraindications for the administration of anti-K19 vaccine and vaccination is recommended for patients with MPN, but we have to clarify that this is the average vaccination rate for Bulgaria. Studies pointed out that all patients with MPN should receive vaccine against COVID-19 [11].

The risk of infection varies between different subtypes of MPN. A European Leukaemia Net (ELN) study reported that 175 COVID 19 patients from 38 haematology centres were analysed from February to May 2020. Among the MPN patients, the COVID 19 group of patients with primary myelofibrosis (PMF) in this study, including pre-PMF and overt PMF, was the majority and accounted for 44% of reported cases [12]. Patients with MPN and especially with MF are at increased risk of infections and thrombotic events [5, 13]. This is also observed in the group monitored by us, in which patients with MF and COVID 19 were found to be 45.7% of the total group, but only one thrombotic event was found (6.2% of all infected). ELN publishes study results on incidence and risk factors for thrombosis and bleeding. It included 162 patients, of which with ET (n=48), PV (n=42), PMF (n=56) and pre-PMF (n=16). There were 22 cases of significant thrombosis (n=15) and significant haemorrhages (n=7) that occurred during the acute phase of coronavirus infection [14, 15].

A GIMEMA study analysed patients with MPN and COVID 19 for the period from January 2020. until June 2021. 11,276 patients with MPN were included, divided into 2111 with MF, 3543 with PV and 5622 with ET. MF patients diagnosed with COVID 19 are 19.4%. According to the course of the disease, 27.7% are asymptomatic/mild, 33.6% have moderate-severe disease, and 38.7% have severe disease. Mortality in patients with MF is 17.5%. ($p < 0.0001$) [16]. In our study group, according to the severity of the course, most of the patients had COVID 19 with mild or moderate-severe symptoms. The data on the severity of the flow do not fully match the results of the GIMEMA study. This can be explained both by the volume of followed patients and by the characteristics of the group, because in our population, all patients were treated with ruxolitinib.

In the SBALHZ observed group, all patients were on ruxolitinib treatment at the start of observation. There is no difference in the severity of the course of the disease related to the daily dose of the drug. In the GIMEMA study, ruxolitinib treatment was discontinued due to COVID 19 in 3.4% of asymptomatic and 1.3% of symptomatic patients; 31% of asymptomatic patients reduced the dose. As of June 2021, the same study analysed the administered vaccines: 72.3% of MPN patients received an mRNA vaccine and only 8% a vector vaccine. 77.1% of the vaccinated are from the first category with MF. After the vaccine, 1.5% of MPN patients tested positive for COVID 19, and 3.4% of them had MF [16]. According to other studies, it is not recommended to stop treatment with a JAK inhibitor if you test positive for coronavirus. If it is necessary to stop the treatment, it should happen with a gradual reduction of the dose to avoid a withdrawal syndrome [17, 18]. The continuation of the treatment of MPN in the diagnosis of COVID 19 has been studied. The results showed that Hydroxyurea (HU) showed no significant correlations. On the other hand, the analysed data showed an increased risk of death in patients who abruptly stopped ruxolitinib treatment [12].

Some studies reported that JAK inhibitors and especially ruxolitinib were tested to counteract viral load and its complications such as cytokine storm, but the results are inconclusive or show no benefits [19 - 21]. The other studies conclude that ruxolitinib is effective in patients with COVID 19, treatment is feasible and can be beneficial in patients with COVID-19 pneumonia, could preventing cytokine storm and adverse drug reactions [22]

A limitation of the present study is that it was conducted in only one hospital, but it is specialized in the treatment of haematological diseases and treats patients from all over the country, so we can consider the study to be representative

of the population. It is also necessary to consider that MF is a rare diagnosis, and this determines the small number of observed patients.

5. Conclusion

Patients with MF have COVID 19 more often than the general population. Mortality in the observation group was higher compared to the general population but comparable to published data for patients with MF. The disease is more often mild or medium-severe. Vaccination coverage is comparable to that of the general population.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interests to be reported.

Statement of ethical approval

The study was approved by the local ethic committee of the hospital.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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