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Predictors of poor outcome in tocilizumab treated patients with Sars-CoV-2 related severe respiratory failure: A multicentre real world study

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1. Introduction

Severe respiratory failure represents the most feared manifestation of SARS-CoV2 infection with potential devastating consequences, independently from the different pandemic waves and virus variants. Despite significant progress in the prevention of SARS-CoV2 infection by using different strategy such as closure of activities and borders, movement restriction, social distancing and vaccination, appropriate management of SARS-CoV2 related severe respiratory failure remains a cumbersome problem in clinical practice and for the healthcare systems [1,2]. Cytokine storm represents the cornerstone of respiratory failure associated with pulmonary damage in SARS-CoV2 infection [3]. In fact, evidence shows that once bronchial epithelial cells, alveolar pneumocytes and pulmonary capillary endothelial cells are infected by SARS-CoV2 by leakage with ACE2 receptor, pro-inflammatory molecules are released by infected cells and alveolar macrophages, in addition to recruited T lymphocytes, monocytes, and neutrophils. As a consequence, pulmonary oedema fills the alveolar spaces followed by hyaline membrane formation. Moreover, anomalous coagulation is activated by the inflammatory and immune process leading to formation of microthrombi and subsequent thrombotic sequelae. The dysregulation of inflammatory, immune and coagulation processes is mediated by pro-inflammatory cytokines or enzymes such as Tumor Necrosis Factor, Interleukins, Janus Kinase (JAK) by signal transducer and activator of transcription (STAT) pathway and Interferon [4]. Interleukin-6 (IL-6) plays a pivotal role in the SARS-CoV2 related cytokine storm. Evidence shows that high levels of IL-6 are associated with severe COVID-19 and it has been demonstrated that IL-6 is an optimal prognosticator in SARS-CoV2 related respiratory failure [5]. Blocking the cytokine cascade at different points, the dysregulation of inflammatory, immune and coagulation systems could be avoided and pulmonary damage limited reducing the risk of respiratory failure progression. Therefore it’s not surprising that research has focused on molecules aimed to avoid or extinguish the SARS-CoV2 related cytokine storm, such as Interleukin-1 (Anakinra) or IL-6 (Tocilizumab, Sarilumab) antagonists or JAK-STAT inhibitors (Baricitinib, Ruxolitinib) [6]. The IL-6 inhibitor Tocilizumab is a humanized monoclonal antibody which binds both with membrane bound and soluble receptors for IL-6 so blocking the signal transduction by which the JAK-STAT is activated perpetrating the cytokine storm [7].

Tocilizumab has shown to be effective and safe in reducing the progression to severe pulmonary damage and improve prognosis of coronavirus disease (COVID)-19 patients [8]. Meta-analyses showed that Tocilizumab significantly reduce the relative risk of 30-day mortality of around 10-15% and the risk of mechanical ventilation of around 20-26%, without increasing the risk of infection and/or adverse events [9,10]. Based on favourable evidence, international guidelines suggest to use Tocilizumab in patients with severe SARS-CoV-2 related respiratory failure [11]. Despite this evidence, 30-day mortality and invasive mechanical ventilation risks in patients treated with Tocilizumab remain not negligible, being 24.6% and 10.3% respectively in randomized clinical trials, and 25.5% and 17.1% respectively in cohort studies [9]. Risk factors for mortality and/or Intensive Care Unit (ICU) admission with need for oro-tracheal intubation (OTI) in COVID-19 patients treated with Tocilizumab remain uncertain, therefore the aim of this study was to investigate on predictors of poor outcome in Tocilizumab treated patients in the real world practice.

2. Materials and methods

We retrospectively analyzed demographic, clinical, laboratory and chest computer tomography (CCT) data of COVID-19 patients admitted to Internal Medicine or Infectious Diseases wards of Azienda USL Toscana Centro, Tuscany, Italy (see supplemental materials for details) and suffering from severe SARS-CoV-2 related respiratory failure firstly not requiring ICU admission after Emergency Department triage who were treated with Tocilizumab.

Severe respiratory failure was defined according to Infectious Diseases Society of America (IDSA) as pulsossimetry ≤ 94% on room air, including patients on supplemental oxygen [12]. All patients received intravenous (8 mg per kilogram of actual body weight, up to a maximum of 800 mg over a period of 1 hour) or subcutaneous (324 mg) Tocilizumab in unique administration according to RE-MAP and RECOVERY randomized controlled trials (RCTs) and previous studies [13–15]. According to IDSA guidelines [12], European Medical Agency (EMA) [16] and Italian Agency of Drug (AIFA) [17], indications for Tocilizumab administration in patients admitted to non ICU settings were: i)
hospitalized patients with C-reactive protein (CRP) ≥7.5 mg/dL and ii) rapid progression of respiratory failure after 24-48 hours from hospital admission despite standard treatment by dexamethasone or other steroids, and requiring FiO2 increasing. Local additional criteria endorsed by the study group of Azienda USL Toscana Centro foresaw that Tocilizumab should be administered only if PaO2/FiO2 ratio (P/F) was ≤ 250. Exclusion criteria were severe immunodepression secondary to diseases or pharmacological treatment, liver failure (alanine amino transferase over five fold the upper limit), high risk of gastrointestinal perforation, concomitant viral, bacterial or fungal infection with sepsis, neutropenia (neutrophils count < 0.5 × 10^9/L), thrombocytopenia (platelets count < 50 × 10^9/L), documented hypersensitivity to Tocilizumab and P/F > 250. For all patients, age, sex, co-morbidities, home-treatments, symptoms onset before hospitalization and vital signs, such as Glasgow Coma Scale (GCS), body temperature, respiratory rate, heart rate, systolic blood pressure, room air pulseoximetry oxygen saturation (RAO2), P/F measured at hospital admission and P/F at the day of Tocilizumab administration were recorded. The use of respiratory support by using non invasive ventilation (NIV), CPAP-helmets and high flow nasal cannula (HFNC) alone or alternate during the hospital stay was registered. Concomitant pharmacological treatment with dexamethasone and its dosage, remdesivir, antibiotics, standard or intermediate prophylactic dose of low-molecular weight heparins (LMWHs) were also recorded. Neutrophils, lymphocytes and platelets counts, IL-6, D-Dimer, fibrinogen, CRP, lactate dehydrogenase (LDH), procalcitonin, activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR) levels, Neutrophils/Lymphocytes (N/L) and IL-6/Lymphocytes (IL-6/Lym) ratios measured at hospital admission were collected. Computed tomography ground glass opacities (CT-GGO) were independently analyzed by two Pneumologists. Pulmonary surface involvement was classified into three grades: low (< 25%), moderate (20-50%), severe (> 50%). The primary endpoint was the combination of in-hospital mortality and/or ICU admission with orotracheal intubation (OTI). We compared patients who died and/or were admitted to ICU undergoing OTI with those who did not. The study was approved by the local Ethical Committee.

For statistical analysis continuous variables were reported as mean ± standard deviation (SD). In the univariate analysis, categorical variables were compared by using the Fisher exact test. Multivariate logistic regression analysis was used to estimate Odds Ratios (ORs) and their 95% confidence interval for the combination of in-hospital mortality and/or ICU admission with orotracheal intubation (OTI). We compared patients who died and/or were admitted to ICU undergoing OTI with those who did not. The study was approved by the local Ethical Committee.

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### 3. Results

Two hundreds and eighty-seven patients (29.9% females) with mean age ± SD 64.1 ± 12.6 years were the study population. In-hospital mortality was 18.8%, while 11.5% of patients required ICU admission with OTI. The composite endpoint in-hospital mortality and/or ICU admission with OTI occurred in 23.7%. Mean length of hospital stay (LOS) was 19.5 ± 11.9 days. Mean number of days since symptoms onset to hospital admission was 6.4 ± 4.2. Mean P/F at hospital admission was 250.6 ± 81.2, while mean P/F at the day of Tocilizumab administration was 139.1 ± 52.9. Two hundreds and twenty-nine patients (80.5%) were treated with respiratory support by using NIV, CPAP-helmets and/or HFNC. Table 1 summarizes the characteristics of the study population.

Patients who died and/or were admitted to ICU with OTI were significantly older (71.3 ± 11.2 vs 61.9 ± 12.2, p < 0.0001), had a significantly more frequent history of blood hypertension and chronic renal failure and, overall, they had a significantly more frequent history of at least one or more chronic diseases. Moreover, the use of antiplatelet agents as home treatment was significantly more prevalent in patients who died and/or were admitted to ICU with OTI compared with those who did not. Table 2 shows the difference in comorbidity and home-treatments between the two analyzed subgroups. No difference was found comparing the mean number of days since symptoms onset to hospital admission between the two subgroups (6.8 ± 4.2 days in patients who died and/or were admitted to ICU with OTI vs 6.3 ± 4.2 days in patients who did not, p = 0.3919). Median time for starting respiratory support from ward admission by using HFNC, CPAP-helmets and/or NIV

### Table 1

Characteristics of study population.

| Characteristic                  | Alive and/or not admitted to ICU | Dead and/or admitted to ICU with OTI | p      |
|--------------------------------|----------------------------------|-------------------------------------|--------|
| Number                         | 287                              | 219 pts                             |        |
| Females                        | 86 (29.9%)                       | 17 (25%)                            | 0.0381 |
| Males                          | 201 (70.1%)                      | 0.972                               |        |
| Mean age ± SD (years)          | 64.1 ± 12.6                      | 71.3 ± 11.2                         | < 0.0001 |
| Mean LOS ± SD (days)           | 19.5 ± 11.9                      | 6.4 ± 4.2                           | 0.2907 |
| Number of days since symptoms onset before hospital admission (mean ± SD, days) | 6.4 ± 4.2 | 0.3919 |
| Mean P/F at hospital admission | 250.6 ± 81.2                     | 139.1 ± 52.9                        |        |
| Respiratory support by NIV, CPAP-helmets and/or HFNC | 229 | 0.0002 |
| Mean P/F at the day of Tocilizumab administration | 139.1 ± 52.9 | 0.0002 |
| In-hospital mortality          | 54 (18.8%)                       | 9 (13.2%)                           |        |
| ICU admission                  | 69 (24.0%)                       | 33 (11.5%)                          |        |
| Without OTI                    | 36 (12.5%)                       | 27 (11.6%)                          |        |
| With OTI                       | 33 (11.5%)                       | 7 (2.9%)                            |        |
| In-hospital mortality and/or ICU admission with OTI | 68 (23.7%) | 0.0001 |
| In-hospital mortality in patients admitted in ICU | 29 (42.0%) | 0.0001 |

Legend: LOS= lenght of hospital stay; P/F= PaO2/FiO2 ratio; HFNC= high flow nasal cannula; ICU= Intensive Care Unit; OTI= oro-tracheal intubation; NIV= non-invasive ventilation.

### Table 2

Co-morbidities. Comparison between patients dead and/or admitted to ICU with OTI and patients alive and/or not admitted to ICU.

| Co-morbidities        | Alive and/or not admitted to ICU | Dead and/or admitted to ICU with OTI | p     |
|-----------------------|----------------------------------|-------------------------------------|-------|
| Demographics          |                                   |                                     |       |
| Mean age ± SD         | 61.9 ± 12.2                      | 71.3 ± 11.2                         | < 0.0001 |
| Mean age ± SD Females | 62 (28.3%)                       | 24 (35.2%)                          | 0.2907 |
| Mean age ± SD Males   | 157 (71.7%)                      | 44 (64.8%)                          |       |
| Mean age ± SD         |                                   |                                     |       |
| Blood hypertension    | 90 (41.0%)                       | 46 (67.6%)                          | 0.0002 |
| Cardiovascular diseases | 36 (16.4%)                     | 17 (25%)                            | 0.1511 |
| Diabetes              | 33 (15.0%)                       | 13 (19.1%)                          | 0.4508 |
| Chronic pneumopathies | 15 (6.8%)                        | 9 (13.2%)                           | 0.1294 |
| Renal failure (creatinine clearance < 50 ml/min) | 7 (3.2%) | 0.0040 |
| Chronic inflammatory diseases | 2 (0.9%)                     | 2 (2.9%)                            | 0.2390 |
| Dementia              | 5 (2.3%)                         | 4 (5.8%)                            | 0.2231 |
| Cancer                | 3 (1.3%)                         | 2 (2.9%)                            | 0.3394 |
| Stroke                | 27 (12.3%)                       | 11 (16.1%)                          | 0.4167 |
| At least one of the abovementioned co-morbidities | 126 (57.5%) | 0.0010 |
| Home-treatment        |                                   |                                     |       |
| ACE inhibitors/sartans | 55 (25.1%)                      | 24 (35.2%)                          | 0.1201 |
| DOAC/VKA              | 10 (4.5%)                        | 7 (10.2%)                           | 0.1358 |
| Antiplatelet agents   | 30 (13.6%)                       | 17 (25%)                            | 0.0381 |

Legend: DOAC=direct oral anticoagulant; VKA= vitamin K antagonist; ICU= Intensive Care Unit; OTI= oro-tracheal intubation; SD=standard deviation.
was 1 (IQR 1-3) day in patients who died and/or were admitted to ICU with OTI, while it was 2 (IQR 1-3) days in those who did not. No significant difference was found in respiratory support by NIV, CPAP-helmets and/or HFNC between the two subgroups (78% in patients who died and/or were admitted to ICU vs 80.4% in those who did not, p=0.7298). All patients admitted to ICU received respiratory support by NIV, CPAP-helmets and/or HFNC in the days or hours before ICU admission.

CT-GGO involving the pulmonary surface \( \geq 50 \% \) were found in 55.4% of patients who died and/or were admitted to ICU with OTI and in 21.5% of patients who did not (p=0.0001). In patients alive and/or not admitted to ICU CT-GGO involving \(< 25 \% \) of pulmonary surface were significantly more prevalent (27% vs 4.2%, p=0.0005) (Table 3).

Mean values of creatinine, CRP and procalcitonin were significantly higher and lymphocytes count significantly lower in patients who died and/or were admitted to ICU with OTI compared with those who did not (Table 4), while for the other biomarkers no significant differences were found. RAO\(_2\)S (81.8% vs 89.1%, p=0.0055) and P/F at hospital admission (220.7 vs 261.5, p=0.0249) were significantly lower in patients who died and/or were admitted to ICU with OTI compared with those who did not, while no difference was found in P/F at the day of Tocilizumab administration between the two subgroups (132.8 vs 141.0, p=0.2664) (Table 5).

In patients who died and/or were admitted to ICU with OTI the use of antibiotics was significantly more frequent, while the use of remdesivir was significantly more frequent in patients who survived and/or were not admitted to ICU. No difference between the two groups was found regarding the route of Tocilizumab administration (intravenous or subcutaneous), dexamethasone dosage and in the use of standard or intermediate dose LMWHs (Table 6).

No significant difference was found between the two groups regarding the rate of symptomatic venous thromboembolism events (5.8% in patients who died and/or were admitted to ICU with OTI)

### Table 3

Computer tomography at hospital admission. Comparison between patients dead and/or admitted to ICU with OTI and patients alive and/or not admitted to ICU.

| Parameter | Alive and/or not admitted to ICU | Dead and/or admitted to ICU with OTI | p     |
|-----------|---------------------------------|--------------------------------------|-------|
| Performed | 164 (74.8%)                     | 51 (75%)                             | 1.000 |
| Data available | 159                     | 47                                   |       |
| Parenchymal involvement | Mild (< 25%) | 43 (27%) | 2 (4.2%) | 0.0005 |
| | Moderate (25-50%) | 82 (51.5%) | 19 (40.4%) | 0.1863 |
| | Severe (> 50%) | 34 (21.5%) | 26 (55.4%) | 0.0001 |

Legend: ICU=Intensive Care Unit; OTI=oro-tracheal intubation.

### Table 4

Laboratory. Comparison between patients dead and/or admitted to ICU with OTI and patients alive and/or not admitted to ICU.

| Parameter                  | Alive and/or not admitted to ICU | Dead and/or admitted to ICU with OTI | p     |
|---------------------------|---------------------------------|--------------------------------------|-------|
| Neutrophils 10\(^3\)/μL   | 9.2                             | 7.3                                 | 0.6167|
| Lymphocytes 10\(^3\)/μL   | 0.9                             | 0.6                                 | 0.0086|
| Neutrophils/Lymphocytes ratio | 11.5                           | 10.8                                | 0.8570|
| Creatinine mg/dL          | 9.0                             | 8.2                                 | <0.0001|
| Lactate dehydrogenase U/L | 531.0                           | 572.1                               | 0.2375|
| C-reactive protein mg/dL  | 8.5                             | 5.1                                 | <0.0001|
| Procalcitonin ng/ml       | 0.1                             | 0.1                                 | 0.0002|
| Interleukin-6 pg/ml       | 76.6                            | 77.9                                | 0.9346|
| Interleukin-6/Lymphocytes ratio | 113.9                        | 124.7                               | 0.6370|
| D-DIMER microg/L          | 1547.7                          | 4179.0                              | 0.1544|
| Fibrinogen mg/dL          | 773.0                           | 727.6                               | 0.0964|
| Activated partial         | 31.3                            | 31.1                                | 0.8226|
| thromboplastin time (aPTT) (sec) | 1.4                         | 3.7                                 | 0.6568|
| International Normalized Ratio (INR) | 1.4                        | 3.7                                 | 0.6568|
| Platelets 10\(^3\)/μL     | 203.5                           | 71.8                                | 0.0692|

Legend: ICU=Intensive Care Unit; OTI=oro-tracheal intubation; SD=standard deviation.

### Table 5

Vital signs and respiratory indexes. Comparison between patients dead and/or admitted to ICU with OTI and patients alive and/or not admitted to ICU.

| Parameter                  | Alive and/or not admitted to ICU | Dead and/or admitted to ICU with OTI | p     |
|---------------------------|---------------------------------|--------------------------------------|-------|
| GCS                       | 15                              | 0                                    | 1.000 |
| Body temperature (°C)     | 37                              | 37                                   | 0.8    | 1.000 |
| RR (breaths per minute)   | 21                              | 7.4                                 | 0.4431|
| HR (beats per minute)     | 88                              | 16                                   | 0.6436|
| SBP (mmHg)                | 129                             | 20.8                                | 0.2912|
| P/AO\(_2\) (%)            | 89.1                            | 15.6                                | 0.0055|
| P/F                       | 261.5                           | 141                                 | 0.0249|

Legend: GCS=Glasgow Coma Scale; RR=respiratory rate; HR=heart rate (bpm=beats per minute); SBP=systolic blood pressure; P/AO\(_2\) = room air pulse oximetry oxygen saturation; P/F=pAO\(_2\)/FiO\(_2\) ratio; ICU=Intensive Care Unit; OTI=oro-tracheal intubation; SD=standard deviation.

### Table 6

Concomitant pharmacological treatment. Comparison between patients dead and/or admitted to ICU with OTI and patients alive and/or not admitted to ICU.

| Parameter                  | Alive and/or not admitted to ICU | Dead and/or admitted to ICU with OTI | p     |
|---------------------------|---------------------------------|--------------------------------------|-------|
| Tocilizumab               | 182 (83.1%)                     | 54 (79.4%)                           | 0.4731|
| Intravenous               | 37 (16.9%)                      | 14 (20.6%)                           |       |
| Subcutaneous              | 39 (57.3%)                      | 29 (42.6%)                           | 0.7794|
| Dexamethasone Standard dose (6-8 mg) | 130                      | 39 (57.3%)                           | 0.7794|
| High dose (16-20 mg)      | 89 (40.7%)                      | 29 (42.6%)                           | 0.0015|
| Remdesivir                | 42 (19.1%)                      | 5 (7.3%)                             | 0.0236|
| Antibiotics               | 152 (69.4%)                     | 55 (80.8%)                           |       |
| Low molecular weight heparins | Standard dose (enoxaparin 40 mg once per day) | 172 (78.5%) | 51 (75%) | 0.6170|
| Intermediate dose (enoxaparin 60 mg once per day or 40 mg twice per day) | 47 (21.5%) | 17 (25%) |       |

Legend: ICU=Intensive Care Unit; OTI=oro-tracheal intubation; SD=standard deviation.
Table 7
Risk factors for death and/or Intensive Care Unit admission with oro-tracheal intubation. Multivariate analysis by logistic regression.

| Variable                                | Odds ratio | 95% CI        |
|------------------------------------------|------------|---------------|
| Age over 65 years                        | 17,347     | 3,7133-81,0443|
| History of blood hypertension            | 3,0935     | 0,7088-13,5021|
| History of renal failure (CrCl ≤ 50 mL/min) | 9,5873    | 0,4332-212,1814|
| Co-morbidity (at least one between history of tobacco use, cardiovascular diseases, chronic pneumoanphies, blood hypertension, diabetes, renal failure, chronic inflammatory diseases, cancer, dementia and/or other neurological diseases) | 1,4449 | 0,2763-7,5556 |
| Home treatment with antiplatelets agents  | 1,2261     | 0,2736-5,4951 |
| CRP ≥ 11.4 mg/dL                         | 0,5600     | 0,1284-2,4431 |
| Procalcitonin ≥ 0.14 ng/mL               | 9,9599     | 1,7670-56,1716|
| P/F at hospital admission ≤ 260         | 0,7386     | 0,1805-3,020 |
| RAO-S ≤ 90%                             | 4,6163     | 1,2468-17,0928|
| Concomitant treatment with Remdesivir    | 0,2115     | 0,0350-1,2764 |
| Concomitant treatment with Antibiotics    | 1,0572     | 0,2281-4,9011 |
| CT-GGO involving ≥ 50% of pulmonary surface | 5,1992 | 1,2813-21,0971 |
| Creatinine > 1.15 mg/dL                  | 0,1373     | 0,0203-1,070 |
| Lymphocytes count ≤ 0.8 10^3/μL          | 1,4261     | 0,4028-5,0487 |

Legend: CI=confidence interval; CrCl=creatinine clearance; CRP=C reactive protein; P/F=paO2/FiO2 ratio; SpO2=oxygen pulsosimetry; CT=computer tomography; GGO=ground glass opacities; RAO-S=room air pulsosimetry oxygen saturation.

5.4% in patients who did not, p=1.000) and sepsis (8.8% vs 3.2%, respectively, p=0.0867). Incidence of sepsis was not significantly different in patients who died compared with survivors (9.2% vs 3.8%, p=0.1504).

At multivariate analysis, age ≥ 65 years (OR 17.3, 95% CI: 3.7-81.0), procalcitonin ≥ 0.14 (OR 9.9, 95%CI: 1.7-56.1), RAO-S ≤ 90% (OR 4.6, 95%CI: 1.2-17.0) and CT-GGO involvement ≥ 50% (OR 5.1, 95%CI: 1.2-21.0) resulted independent risk factors associated with poor outcome (death and/or ICU admission with OTI) (Table 7).

4. Discussion

Severe respiratory failure associated with SARS-CoV-2 infection is burdened by high mortality and/or need for OTI [18]. Thus, appropriate prevention and management of severe SARS-CoV-2 related respiratory failure is fundamental in clinical practice to avoid poor outcome. SARS-CoV-2 infection can determine severe pulmonary damage leading to acute respiratory distress syndrome (ARDS) due to inflammation, immune system and coagulative cascade activation, in whom the cytokine reaction seems to play the main role [19-20]. Drugs blocking the cytokine storm such as IL-1 or IL-6 antagonists have been investigated accumulating evidence for this purpose [8]. Tocilizumab is the most studied IL-6 antagonists in the context of COVID-19. Overall, evidence deriving from RCTs and cohort studies is favourable, demonstrating that Tocilizumab added on standard treatment significantly reduces 30-day mortality and needing for OTI, without serious adverse events such as sepsis and/or hepatitis or tuberculosis recurrence [9,10,21]. Despite this efficacy, a not negligible percentage of patients with severe SARS-CoV-2 respiratory failure treated by Tocilizumab dies or undergoes OTI due to respiratory deterioration. A recent meta-analysis including around 3350 COVID-19 patients receiving Tocilizumab in RCTs showed that 30-day mortality was 25.3%, ranging from 27.6% in patients with severe infection to 9.6% in non-severe infection [9]. Moreover, this meta-analysis showed a 30-day incidence of mechanical ventilation of 14.8%, ranging from 16.7% in severe infection to 7.6% in non severe infection [9]. Therefore, studies aimed to identify factors influencing the response to Tocilizumab seem warranted. We performed a real-world clinical practice retrospective multicentre study aimed to focus on risk factors associated with in-hospital mortality and/or ICU admission with OTI in COVID-19 patients firstly admitted to non ICUs and suffering from severe respiratory failure treated with Tocilizumab. We found that patients who had poor outcome such as death and/or ICU admission with OTI were older and co-morbid, had higher creatinine, CRP and procalcitonin values and lower lymphocytes count, P/F and RAO-S, major CT-GGO involvement at hospital admission and received antibiotics and remdesivir in higher and lower percentages, respectively. Age ≥ 65 years, procalcitonin ≥ 0.14 ng/mL, RAO-S ≤ 90% and CT-GGO involvement ≥ 50% were independent risk factors of poor outcome (death and/or ICU admission with OTI). Our findings confirm that comorbidity and more severe clinical and radiological manifestations are associated with poor outcome and add information about predictors of Tocilizumab failure in severe SARS-CoV2 patients. In a meta-analysis enrolling more than seventeen million of people, Booth A. et al. found that age >75, male sex, severe obesity, active cancer, symptoms such as myalgia and dyspnoea and vital signs such as respiratory rate and RAO-S were associated with increased risk of severe outcome [22]. In a systematic review, Dessie ZG et al found that in-hospital mortality of SARS-CoV2 patients was associated with advanced age, chronic obstructive pulmonary disease, cardiovascular disease, diabetes, hypertension, obesity, cancer, acute kidney injury and increased D-Dimer levels [23]. Kim L. et al. found as independent factors associated with ICU admission age over 50 years, male sex, obesity, immunosuppression and diabetes, while age over 50 years, male sex, immunosuppression, renal disease chronic lung disease, cardiovascular disease, neurologic disorders and diabetes were associated with in-hospital mortality [24]. In severe SARS-CoV2 patients, Grasselli G. et al. found as independent risk factors associated with mortality older age, male sex, high FiO2, low P/F and history of chronic obstructive pulmonary disease, hypercholesterolemia and diabetes [25]. Moreover our findings confirm no advantage on outcome from combination of Tocilizumab plus Remdesivir and from the co-administration of Tocilizumab with antibiotics [26,27]. A possible reason for explaining the lack of effectiveness of antibiotics is that the rate of co-infections in COVID-19 seems low, despite systematic reviews show that procalcitonin values over 0.05 ng/mL are associated with severe SARS-CoV2 infection [27,28].

Previous studies have investigated on factors influencing the response to Tocilizumab in COVID-19 patients. In the RCT with the largest sample size, the RECOVERY RCT, Tocilizumab resulted significantly superior to standard treatment in male sex, white ethnicity, in patients with symptoms onset < 7 days before administration, and in those receiving corticosteroids as concomitant treatment [15]. In a study enrolling eighty-seven COVID-19 patients treated by Tocilizumab, Emre Eskazan A et al. found that platelets count, procalcitonin, D-Dimer levels, RAO-S and the time from symptoms onset to Tocilizumab administration were associated with 28-day mortality of 16.1%. The Authors combined these variables in the CERRAHPASA-PREDICT score, whose positive and negative predictive values were 94.5% and 92.9%, respectively [29]. In another study enrolling two-hundreds and sixty-six COVID-19 patients treated with Tocilizumab, Mussini C et al. identified sex, day-4, P/F after Tocilizumab administration, platelets count and CRP as independent risk factors for treatment failure and associated with 28-day mortality and mechanical ventilation [30]. In their study 28-day mortality was 10%, while 15% of patients underwent mechanical ventilation. Combining these variables, the Authors proposed a predictive score with an area under the receiving operating curve of 0.80 [30].
In one hundred and twenty COVID-19 patients treated with Tocilizumab, Sarabia de Ardanaz L et al. found that patients who died had significantly higher values of lactate dehydrogenase, CRP, troponin I, lower levels of platelets and lymphocytes and lower P/F [31]. Desai HD et al. reported their experience in Asian Indians COVID-19 patients treated with Tocilizumab [32]. The Authors found age, the presence of type-2 diabetes, cancer, in-hospital complications, such as acute kidney injury, sepsis/septic shock, multiorgan dysfunction, and D-dimer values > 5,000 ng/mL [32] as predictors of mortality. Lohse A et al. in about thirty COVID-19 patients treated with Tocilizumab reported that more pronounced lymphopenia, lower platelet counts, lower fibrinogen levels, higher aspartate-amino-transferase and greater oxygen request were risk factors for death [33].

The beneficial response to Tocilizumab in COVID-19 patients seems to be associated with restoration of inflammatory, coagulative and immunological biomarkers after its administration [34]. Therefore, following the trend of these biomarkers in response to Tocilizumab could be of the utmost importance for predicting the mortality risk. Literature evidence shows that poor outcome is associated with persistence of high biomarkers values after Tocilizumab administration. Lakatos B et al., in a one hundred and six sample size study on COVID-19 patients treated with Tocilizumab, reported that patients who died had higher values of IL-6 and LDH and insufficient restoration of lymphocytes count at 7 and 14 days after Tocilizumab administration compared with survivors [35]. A lot of evidence shows that different phenotypes of COVID-19 patients with different inflammatory and immune response, mortality risk and response to respiratory support exist [4,36,37]. The failure to Tocilizumab treatment could support this hypothesis, arising the need for identifying factors which could allow to tailor treatments. Which is the optimal pharmacological strategy in patients refractory to Tocilizumab is an unresolved issue. A small sample size study showed no advantage of the IL-1 antagonist Anakinra as rescue treatment in Tocilizumab-refractary patients [38].

Our study has limitations and strengths. Main limitations is secondary to the retrospective methodology. We believe that strengths are the multicentre design, the not negligible sample size and the real world setting.

5. Conclusion

Tocilizumab has shown to improve outcome in patients with severe respiratory failure associated to SARS-CoV-2 related pneumonia. However, a not negligible number of patients die and/or require invasive mechanical ventilation, despite Tocilizumab treatment. Therefore studies focusing on Tocilizumab failure are warranted. In our multicentre study, age ≥ 65 years, procalcitonin ≥ 0.14 ng/mL, RAOS ≤ 90% and CT-GGO involvement ≥ 50% were independent factors associated to poor outcome in this kind of patients. These factors should be taken into account in the clinical practice identifying patients at risk of Tocilizumab failure requiring a more aggressive management and closer monitoring for avoiding a poor outcome.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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