Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection 81 (2020) e61–e66

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Review

How is immunosuppressive status affecting children and adults in SARS-CoV-2 infection? A systematic review

Chiara Minotti[a,*], Francesca Tirelli[a], Elisa Barbieri[b], Carlo Giaquinto[b], Daniele Donà[b]

[a] Department of Women's and Children's Health, University of Padua, via Giustiniani 3, Padua, Italy
[b] Division of Pediatric Infectious Diseases, Department for Woman and Child Health, University of Padua, via Giustiniani 3, Padua, Italy

ARTICLE INFO

Article history:
Accepted 18 April 2020
Available online 23 April 2020

Keywords:
SARS-CoV-2
Children
Adults
Immunosuppression
Cancer
Transplant

SUMMARY

Objectives: SARS-CoV-2 infection has now a global resonance. Data on how COVID-19 is affecting immunocompromised patients are however few. With our study we aimed to systematically review the current knowledge on SARS-CoV-2 cases in children and adults with immunosuppression, to evaluate outcomes in this special population.
Methods: A systematic review of literature was carried out to identify relevant articles, searching the EMBASE, Medline, and Google Scholar databases. Studies reporting data on pre-defined outcomes and related to immunosuppressed adults and children with SARS-CoV-2 were included.
Results: Sixteen relevant articles were identified with 110 immunosuppressed patients, mostly presenting cancer, along with transplantation and immunodeficiency. Cancer was more often associated with a more severe course, but not necessarily with a bad prognosis. Our data show that both children and adults with immunosuppression seem to have a favorable disease course, as compared to the general population.
Conclusion: Immunosuppressed patients with COVID-19 seem to be few in relation to the overall figures, and to present a favorable outcome as compared to other comorbidities. This might be explained by a hypothetical protective role of a weaker immune response, determining a milder disease presentation and thus underdiagnosis. Nevertheless, surveillance on this special population should be encouraged.

Introduction

On a global scale, we have been currently experiencing the effects of SARS-CoV-2 pandemic, started at the end of December 2019 in Wuhan, Hubei Province, China.

With the outbreak reaching a global spread, concern about the possible effects of the infection on the population of immunocompromised patients has raised.[1] Unlike common viral agents, SARS-CoV-2 does not seem to determine a greater disease severity, as for respiratory complications in immunosuppressed patients. Lung tissue damage during infection seems to be worsened by the host innate immune response.[2] Findings from the impact of COVID-19 pandemic on the immunosuppressed population are few, and most of the published studies have reported symptoms and characteristics of infection in adults, with rare evidence on pediatric population with immunosuppression.

Aim of the study

The aim of this study is to systematically review the current knowledge of SARS-CoV-2 infection in children and adults with a condition of immunosuppression, to evaluate outcomes in this special population.

Methods

Criteria for considering studies for this review

Prospective and retrospective studies, systematic and narrative reviews, case series and case reports were included in the review. Every study reporting data on pediatric or adult patients with COVID-19 and solid organ transplantation, cancer, immunodeficiency or any condition implying therapy with multiple immunosuppressants was considered.

The primary outcome measure was the clinical outcome of SARS-CoV-2 infected adults and children with immunosuppression, including mortality and/or Intensive Care Unit (ICU) admission, also considering composite outcomes. The secondary outcome was any difference in the outcome between cancer and transplant recipient patients.

* Corresponding author: Department of Woman and Child Health, via Giustiniani 3, University of Padua, Padua, (Italy).
E-mail address: minotti.chiara@gmail.com (C. Minotti).

https://doi.org/10.1016/j.jinf.2020.04.026
0163-4453/

Table 1
Characteristics of the included studies.

	Country	Patients	Primary Outcome Measure	Cancer	Transplant	Immunodeficiency
Aslam et al.[4] reviewing Li at al.	China	2	mortality		2 (0 dead)	
D'Antiga[1]	Italy	3 (children)	mortality		3 (0 dead)	
Guan et al.[19]	China	12*	mortality	10 (1 dead)		2 (0 dead)
Guan et al.[16]	China	21	1)Mortality 2)ICU/invasive ventilation	18 (3 dead, 4 ICU/ invasive ventilation)		3 (0 dead)
Guillen et al.[14]	Spain	1	ICU		1 (1 ICU)	
Huang et al.[6]	China	1	mortality	1 (0 dead)		
Korean Society of Infectious Diseases[7]	Korea	8	mortality	7 (7 dead)	1 (1 dead)	
Lescure et al.[8]	France	1	mortality	1 (1dead)		
Liang et al.[17]	China	18	ICU/mortality	18 (9 dead)		
Ludvigsson[9]	China	1 (child)	mortality	1 (0 dead)		
Tian et al.[10]	China	2	mortality	2 (0 dead)		
Wang et al.[15]	China	4	ICU	4 (1 ICU)		
Yang et al.[11]	China	2	mortality	2 (1 dead)		
Yu et al.[12]	China	4	mortality	4 (0 dead)		
Zhang et al.[18]	China	28	1)Mortality 2)in-hospital 3)discharged	28 (8 dead)		
Zhou et al.[13]	China	2	mortality	2 (2 recovered)		

* not specified if also children were included in this subgroup; 9 children in the reported cohort of COVID-19 patients

Data source and search strategy

A systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[3] MEDLINE (Ovid MEDLINE(R) ALL 1946 to March 31, 2020) EMBASE (1996 to 2020 Week 13) and Google Scholar databases were systematically searched, using free text terms for children AND adults AND immunosuppression AND SARS-CoV-2. Moreover, reference list from eligible articles was reviewed to identify other potential relevant studies. The last search conducted was on March 31st 2020. The full search strategy and the flow chart for study selection are available in the *Supplementary material figures*.

Studies reporting data on 1) pre-defined outcomes (need for intensive care unit, mortality, recovery, composite outcomes) and related to 2) immunosuppressed adults and children affected by 3) SARS-CoV-2 were included. Studies reporting data on SARS-Co-V and MERS-Co-V outbreaks or on patients, children and adults, without mention of immunosuppression, were excluded.

Studies published in languages other than English were excluded.

Two reviewers (CM and DD) independently screened the titles, abstracts and full texts of retrieved articles to assess the eligibility of studies for inclusion. Duplicate references were removed and disagreements were resolved by a consensus to generate the final list of papers. Data on study characteristics (study design), participants, and outcome measures were extracted using a specific form designed by one reviewer (CM) and checked by the other reviewer (DD).

Results

Among the 75 papers from EMBASE and Medline search, the 114 from Google Scholar search and 11 more papers identified though manual search, 16 articles were included, with a total of 110 immunosuppressed patients, mostly due to cancer treatments (98 patients, of which one child with leukemia). The remaining patients had immunodeficiency (five) or were transplant recipients: three were children and had undergone liver transplantation, two adults had undergone heart transplantation and two adults kidney transplantation (Table 1).

Table 2
Results – Overall clinical outcomes.

	Total patients *n=110*
Recovered/in-hospital/no ICU *(n, %)*	72 (65.5)
ICU/invasive ventilation *(n, %)*	6 (5.5)
ICU/dead *(n, %)*	9 (8.2)
Dead *(n, %)*	23 (20.9)

Of the 110 patients, 72 (65.5%) recovered (discharged or inpatients) OR did not require intensive care and 6 (5.5%) needed intensive care OR invasive ventilation. On the other side, 9 (8.2%) reached the composite outcome of death OR ICU admission, and 23 (20.9%) died (Table 2). Not all the studies considered a single outcome, such as mortality or ICU admission. There were composite outcomes being reported by some of the papers, as follows (see also Table 1).

Eleven studies considered mortality as a single outcome.

Aslam et al. reviewed Li et al., that reported two cases of SARS-CoV-2 infection in two adult heart transplant recipients from the Hubei province, examining presentation symptoms and outcome. They belong to roughly 200 heart transplant survivors in the province. One had a mild disease course, while the other was inpatient, requiring a protracted hospitalization time due to severe disease, but both recovered. The authors pointed out that the symptoms at onset in these two cases were not dissimilar to those of non-immunosuppressed cases. The first patient had fever and aspecific findings at CT scan, with recovery after few days and showing the same laboratory findings as non-immunosuppressed patients. The second one had immunosuppressive therapy discontinued and was treated with high dose corticosteroids and immunoglobulins. He had a favorable outcome, being discharged without graft loss. The authors concluded that immunosuppression could have possibly decreased the expression of infection, even though transplant patients are all the same exposed to infection because of the elevated efficiency in transmission of SARS-CoV-2.[4]

D'Antiga reported his experience at one of the most important pediatric hepatology and liver transplantation centers in Italy, in one of the current "red zones" of the outbreak. In a pool of at least 200 transplant patients, of which ten children being inpatients, three tested positive for SARS-CoV-2, without clinical pulmonary disease and thus showing a favorable outcome. None of the patients followed at this center was reported for presenting pneumonia in this period. For this reason, the author suggests that immunosuppression may not be a predisposing factor for COVID-19, being instead protective and avoiding damage to the tissues, otherwise caused by a dysregulation in innate immune response. Compared to the general population, the author reviewed data on the current outbreak, with the hypothesis that immunosuppressive status, including transplantation and chemotherapy at any age, may not be a risk factor for a more severe disease course or even death. He concluded that the risk factors for a worse outcome, even for immunosuppressed patients, were the same presented in the general population, including an old age, obesity, diabetes, cardiovascular disease, and thus immunocompromised children and adults appear not to have a greater risk for a more severe pulmonary involvement.[1]

Guan et al. described 1099 patients with confirmed COVID-19, of which 9 were children aged between 0 and 14. Only one of the children was admitted to ICU and all recovered. Comorbidities were described, but not associated to the age of the patients. Ten patients with cancer and two patients with immunodeficiency were reported; it is not known whether children were among them. Only one of them, presenting cancer, died, while the remaining eleven patients had a good prognosis with recovery. Among the patients with cancer, only three presented a severe disease, with only one patient presenting a composite endpoint event, described as admission to an intensive care unit, the use of mechanical ventilation, or death. Both patients with immunodeficiency had a mild disease course and no composite endpoint event. Overall, a primary composite end-point event was registered in 67 patients (6.1%), including 5.0% being admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died. Of the 173 patients with a severe course, 43 patients (24.9%) presented a primary composite end-point event. Among all cases, the cumulative risk of the composite end point was 3.6%; among those with severe disease, the cumulative risk was 20.6%.[5]

Among the first published cohorts describing the clinical features of COVID-19 patients, infection rate and complications incidence appeared less frequently associated with unfavorable outcomes in cancer patients as compared to patients with other comorbidities. Among 41 patients seen before January 2020 by Huang et colleagues in a COVID-19 dedicated hospital,[6] only one presented with malignancy; this patient did not require ICU admission, while cardiovascular diseases and chronic pulmonary obstruction were more frequently associated with the need of intensive care.

The Korean Society of Infectious Diseases published the clinical features of all the 54 fatal COVID-19 cases reported by the Korean Centers for Disease Control (KCDC) up to March 10, 2020.[7] Total cases count in the Country by that date was 7513, thus with an overall mortality rate of 0.7%, lower than other severely affected Countries such as China and Italy by that date. Among the Korean patients who died of COVID-19, which were all adults, malignancy was the fourth most common comorbidity (7 cases, 13%), as common as respiratory and psychological disorders, while cardiovascular disease (59.3%), diabetes (29.6%) and neurological conditions (18.5%) were, again, those most commonly reported. Korean fatal cases also included one immunosuppressed patient due to kidney transplant.

The first cohort of patients with a confirmed diagnosis of COVID-19 reported in Europe (five travelers all of Chinese origin) has been hospitalized in France and described by Lescure and colleagues.[8] Among those, the most critically ill patient reported thyroid cancer as comorbidity. The patient needed ICU admission for respiratory failure, was treated with Remdesivir and died 24 days after disease onset, due to a secondary fungal pulmonary infection and multiorgan failure. Although malignancy was indeed reported as comorbidity, the thyroid cancer was surgically treated 10 years before SARS-CoV-2 infection, and current immunosuppressive treatments of any kind were not specified in the study.

Ludwigsson led a systematic review on SARS-CoV-2 infection in children, pointing out a better outcome after a milder disease course for this population. He reported a prevalence of critical disease in very young children according to several studies, with few patients requiring intensive care, all of which presented pre-existing conditions. Among these, there was one patient being treated with chemotherapy for leukemia, and still with a favorable outcome, in line with the main tendency to recovery in children, despite ICU admission. Only one death of a 14-year-old boy was reported in one of the cited studies, with no mention to possible pre-existing comorbidities.[9]

Tian et al reported the cases of two adults with lung cancer who underwent lobectomies, with retrospective finding of COVID-19, unknown at the moment of intervention, being asymptomatic for pneumonia, in a likely early phase of disease. The first patient was a 84-year-old woman with hypertension and diabetes. After lobectomy, she began presenting respiratory symptoms, with SARS-CoV-2 afebrile pneumonia confirmation on day 24. Despite therapy with antibiotics, oxygen and supportive care, her conditions deteriorated, a do-not-resuscitate order was taken, and she eventually died on day 29. The second patient was a 73-year-old male, with lung adenocarcinoma and treated hypertension. He was discharged after lobectomy; signs of a suspect atypical viral pneumonia were discovered at CT scan on day 2 post-operatively. He was re-admitted on day 9 for becoming symptomatic and febrile. He was treated for COVID-19 and was progressively healed and discharged. The pathological findings of these two cases preceded the development of clinical symptoms and were overlapping ("exudative and proliferative phases of acute lung injury, such as edema, inflammatory infiltrate, type II pneumocyte hyperplasia, and organisation, but without obvious hyaline membrane formation and other long-term processes"), regardless of the different prognosis.[10]

Yang et al. described 52 critically ill COVID-19 patients admitted to ICU in a single-center study.[11] 50% had chronic comorbidities, among whom two were malignancies; of these patients, one died and one recovered. Among the other reported comorbidities, diabetes was more common in the non-survivor group and all patients with reported cerebrovascular disease did not survive.

Yu et al. reported a series of SARS-CoV-2 infected patients among 1524 patients followed an Oncological Hospital in Wuhan. Twelve confirmed diagnosis were made, with an estimated infection rate superior than that found in the general Chinese population at the time the data were collected (0.79% vs 0.37%). Three of the patients presented severe pulmonary disease, of which one received ICU care and three died. The most common malignancy associated with SARS-CoV-2 infection was non-small cell lung carcinoma (NSCLC) and the most severe cases were reported in elderly patients (age >60 years), as frequently as for non-cancer patients. However, only half of the infected patients were currently immunosuppressed due to active chemotherapy/immunotherapy, suggesting a possible role of hospital exposure.[12]

In another retrospective study on 191 adult patients evaluated in two hospitals of Wuhan, Zhou and colleagues identified older age, higher SOFA score and higher D-Dimer values as risk factors associated with mortality in SARS-CoV-2 infections in their multivariable logistic regression analysis. Furthermore, in this cohort, diabetes and cardiovascular comorbidities were common and espe-

cially coronary artery disease was correlated with a higher risk of death. The presence of a carcinoma, instead, was reported only in two patients, both belonging to the survivor group, and this comorbidity was not considered for the univariate logistic regression.[13]

Two studies considered ICU admission as a single outcome.

The case of a 50-year old man that had undergone the third renal transplantation in 2016, with history of splenectomy for immune thrombocytopenia and (EBV)-associated post-transplant lymphoproliferative disease (PTLD), was reported by Guillen and colleagues. The patient presented at first mild gastrointestinal symptoms and fever, and after five days, respiratory symptoms (unilateral pneumonia) testing positive for SARS-CoV-2. On admission, immunosuppressive therapy with tacrolimus and everolimus was discontinuated, and, after 72 hours of supportive and anti-viral treatment, he required invasive ventilation in ICU. He was treated with Lopinavir/Ritonavir, hydroxychloroquine and Interferon Beta. At the time of the report, he was stable, under respiratory supportive therapy. In this patient, COVID-19 had at first an atypical presentation, starting with mild, aspecific symptoms, with a subsequent respiratory involvement, determining a severe disease course, perhaps due to the multiple comorbidities, and in line with the general population.[14]

Wang et al. described a retrospective series of 69 adult patients seen in a Wuhan COVID-19-dedicated hospital between January 16th and January 29th 2020, and compared patients with and without severe hypoxia at presentation (defined by a cutoff limit of SpO2 90%). Patients with malignancy were four, of whom only one had severe hypoxia (7%). Poorer respiratory manifestations were instead noted in patients with cardiovascular disease (36%), diabetes (43%), hypertension (36%) and chronic obstructive pulmonary conditions (14%).[15]

As for the remaining papers, different composite outcomes were considered, that is to say ICU AND mortality; mortality OR ICU/invasive ventilation; mortality OR in-hospital stay OR discharge.

Guan et al. reported in their retrospective study the effects of comorbidities on COVID-19 confirmed adult patients. Of the 1590 examined cases, 399 had at least one comorbidity. In particular, 18 patients had cancer and three immunodeficiency. A composite outcome was considered, including admission to ICU, invasive ventilation or death. While severe cases were likely to have cancer, immunodeficiency was not listed among the main comorbidities found in patients with a worse outcome. It was also demonstrated that, after adjustment for age and smoking status, patients with comorbidities such as Chronic Obstructive Pulmonary Disease (COPD), diabetes, hypertension and malignancy (HR 3.50, 95%CI 1.60-7.64), but not immunodeficiency had a higher probability to reach the composite endpoint, and in particular seven patients with malignancy, of which three died. Also one patient with immunodeficiency reached the endpoint, with no reported deaths. Overall, as compared with patients without comorbidity, those with at least one comorbidity had an HR (95%CI) of 1.79 (95%CI 1.16-2.77) and those with two or more comorbidities of 2.59 (95%CI 1.61-4.17.[16]

According to Liang et al. patients with malignancy could present a higher risk of severe disease due to SARS-CoV-2 infection, with a poor outcome. They established a prospective cohort to monitor cases throughout China. Of 1590 reported cases, 18 had history of cancer, mostly involving the lungs and colon, rectum and colorectum (five patients each), and following breast (three patients), bladder (two patients), adrenal, thyroid cancer and lymphoma (one patient each). Half of this cohort required ICU admission; for them a composite outcome of severe event was considered, that is to say intensive care treatment or death. The remaining patients, that were not admitted to ICU, all recovered, and had a median younger age. The outcome was not related to the current chemotherapy treatment, with four patients in therapy that recovered without a severe course. Overall, 12 patients were cancer survivors in follow-up after primary resection. Compared to patients without cancer, patients with malignancy had an older age, a more likely history of smoking, had more reported polypnea and more severe baseline CT. There were no significant differences in sex, other symptoms at onset, other comorbidities, or baseline x-ray severity.[17]

Table 3
Results –Clinical outcomes of cancer patients vs. transplant recipients.

Cancer patients *(n, %)*	98 (89)	62 recovered/in-hospital/no ICU 5 ICU/invasive ventilation 9 ICU/dead 22 dead
Transplant recipients *(n, %)*	7 (6.4)	5 recovered 1 ICU 1 dead

The largest oncological cohort so far reported has been described by Zhang et al. Twenty-eight adult patients with malignancy were retrospectively enrolled from 1276 COVID-19 cases, mostly male (17/28) and mostly with lung cancer (7/28), all with history of anti-tumor therapy in the 14 days prior to infection. Eight patients became infected as inpatients during anti-tumor treatment, 20 in the community. Eleven cases also showed pre-exisiting comorbidities. Overall, as for the clinical outcomes, ten patients were discharged, ten were still inpatients and eight died. Fifteen had severe events, six required ICU admission. The authors demonstrated that patients that had been treated against the tumor during the previous 14 days had a significantly higher risk of severe event, also confirmed by the multivariate-adjusted Cox proportional hazards model after adjustment for age and gender. Patients with lung cancer in this cohort appeared more prone to develop a rapid disease progression.[18]

As regards the secondary outcome, of the 98 (89%) patients having received cancer treatment 62 recovered OR were inpatients OR required no intensive care, five reached the composite outcome of ICU admission/invasive ventilation, nine the composite outcome of ICU admission/death and 22 died. Among the seven (6.4%) transplant recipients, 5 recovered, 1 was still inpatient in ICU and 1 died (Table 3).

Discussion

In this systematic review, we aimed to report, as primary outcome measure, the prognosis of COVID-19 in immunosuppressed children and adults. Sixteen relevant publications providing single-patient data were included, and 110 immunosuppressed patients were identified, showing an overall better outcome as compared to other comorbidities.

It is known that COVID-19 outbreak is affecting all age-groups, though appearing to be milder in the pediatric population.[20] Among the possible reasons, children have less comorbidities, do not smoke, have a lower expression of ACE2 receptor and present a different inflammatory response, due to the known changes throughout life stages, with higher numbers of B and T regulator cells, involved in immune tolerance and leading to a “less inflammatory” immune response.[2,21] Cytokine storm is held responsible for tissue damage, being possibly determined not only by a failure of immune system but also by a hyper-immune response.[2]

Overall, our results show that malignancy was reported by a higher number of studies as one of the comorbidities with an impact on disease course, while a minor number of reports considered other conditions related to an immunosuppressive status,

such as transplantation and immunodeficiency. It is still unclear how an immunosuppressive status may influence the response to COVID-19, but these preliminary data show that both children and adults with immunosuppression seem to have often a favorable disease course, as compared to the general population.

As for transplanted patients, children and adults alike, the number of recipients is rising along with the number of immunosuppressed patients, including those affected by cancer.[1] Still, since the start of the outbreak data on this special population are strangely few, and so seem to be the immunosuppressed patients being reported as becoming affected by COVID-19. This may be explained by the fact that these patients may actually present a milder disease, that does not justify hospital admission. It may also be an effect of the lock-down policies adopted by most Countries worldwide.

Immunosuppressants strike humoral immunity and neutrophil action, with a generally higher risk of viral infections, with possibly increased severity.[1] As pointed out by Xia and colleagues, the lesson from preceding outbreaks, such as influenza A H1N1, demonstrates that the susceptibility of immunosuppressed hosts to infection is likely, as a greater number of cases was described with time.[22] Influenza, for instance, can determine a more severe course in children younger than five years and adults, especially if over 65 years and with comorbidities. Also individuals on immunosuppressive treatment risk complications of influenza infection.[23,24] However, this does not seem to be true for Human Coronaviruses (HCoVs) infections. As far as it is known, the host response is a major factor contributing to disease severity, with a dysregulation of innate immunity or an excessive response being significant factors for damage to the tissues and organs during the infectious process.[2] According to mortality and morbidity data on SARS-CoV, MERS-CoV and SARS-CoV-2 infections, it seems that an immunosuppressive status alone may not determine a worse prognosis.[1,25] In addition, it seems that bats may be the healthy reservoir in nature of Coronaviruses because of their immune tolerance mechanism.[26,27]

These characteristics might become central in regards to SARS-CoV-2 infection in immunosuppressed patients, as they may show a potential protective effect given by a weaker immune response against the pathogen, with a resulting milder course of disease.[1]

The apparent effect of host immunosuppression on the excessive immune response to the viral trigger may also serve as a model for the development of potentially effective treatments, such as Tocilizumab.[28] Further studies are needed to better understand the initial kinetics of infection and to identify the factors associated to infection progression and the cytopathic effect of the virus with the consequent damage caused to the lungs due to intense inflammatory response. Understanding such elements may be crucial to help and limit damage due to inflammation, granting an adequate respiratory support, while waiting for viral clearance as an effect of immune response and/or antiviral therapy.

The secondary outcome of our study was directed to any difference in the outcome between cancer and transplant recipient patients.

Transplants, chemotherapy or other conditions implying immunosuppressive treatment alone do not appear to be cause of death at any age. Single-patient data from the considered studies showed a general tendency to a positive outcome, and especially for transplant recipients and patients with immunodeficiency, regardless of age, while malignancy was sometimes associated with severe disease, but not necessarily followed by a worse outcome.

Major concern has raised for oncologic patients, generally considered more vulnerable to infections and development of complications. Indeed, cancer patients not only receive highly immunosuppressive therapies, but their treatment regimens are frequently hospital-based, thus causing higher risks of potential exposure to infections. Moreover, in adult patients, older age and other comorbidities are often present.[29] Several protocols and recommendations have been developed in single centers and at national and international level[30,31] often recommending to change or interrupt ongoing treatment in order to reduce immunosuppression and minimize hospital visits and admissions. The potentially severe outcomes for patients with cancer affected by COVID-19 were reported especially by Liang et al.[17] This finding might be explained by the fact that the pool of cancer patients was bigger and these patients are not only immunocompromised but are definitely exposed to a wide range of side effects of anti-tumor therapy. Of course, also the role of age and other underlying comorbidities must be taken into account. Again, the patients with greater disease severity presented the known risk factor for a worse outcome in the general population, such as elderly age, a high BMI, diabetes, cardiovascular disease and male sex, rather than features directly linked to malignancy and its therapy.

This study clearly points out the paucity of data available on immunosuppressed patients, and especially in the pediatric population. Single-patient data were available for 110 cases only.

Although being the first comprehensive review available on the topic, this study has several limitations. Firstly, the limited number of included papers and the very small sample size did not allow to perform any statistical analysis. Secondly, the number of pediatric patients was not comparable to that of adults and the number of transplant recipients and patients with immunodeficiency was too small compared to cancer patients. For this reason, it was not possible to statistically compare outcomes between these sub-groups. As another limit, one of the studies, by Guan et al,[5] reported outcomes by comorbidity and age groups separately, not specifying whether children were present among patients with cancer, leading to possibly incomplete data on the pediatric population. Moreover, we only considered studies published in English, thus studies in Chinese or other languages have necessarily been missed. Lastly, due to the rapid development of the situation worldwide, we cannot exclude the publication of other studies or reports that our search algorithm may have missed.

Conclusions

To our knowledge, this is the first systematic review dealing with the impact of immunosuppression on SARS-CoV-2 infection. To date, state-of-the-art literature on COVID-19 seems to hint at the fact that immunosuppressed hosts may not present a greater risk of an increased severity of disease, compared to the general population. In addition, COVID-19 is now a pandemic, implying that immunosuppressed patients, adults and children, if infected, might become a viral reservoir with all the consequences on viral spread.

It is known that among the pediatric population disease course is often mild, and this seems to be true, regardless of their immunity status.[1,9,32] Also immunosuppressed adults without further comorbidities appear to have no increased risk of a more severe disease. The major risk factors for a worse outcome appear to remain elderly age, obesity, diabetes and cardiovascular problems, along with male sex. For sure, immunosuppressed patients are not immune to COVID-19, and when infected, especially if presenting a mild disease, as it seems to be likely in the majority of cases, they may be underdiagnosed and become an important source for viral shedding. Nevertheless, surveillance on this special population should be encouraged, also taking into account that the current outbreak should not dissuade from performing life-saving procedures like transplantation or starting or continuing therapies such as chemotherapy for cancer, both in children and in adults.

Declaration of Competing Interest

The authors do not have any conflict of interest. No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Funding

This article is not funded by any source.

Ethical approval

Ethical approval was not needed since this article was a review article.

Contributors

All authors have made substantial contributions to the conception, design, collection and interpretation of data for this review, drafted the manuscript, revised it critically for content and approved the final version.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.04.026.

References

1. D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. *Liver Transpl [Internet]* 2020:0–1. Available from http://www.ncbi.nlm.nih.gov/pubmed/32196933.
2. Abdulamir AS, Hafidh RR. The Possible Immunological Pathways for the Variable Immunopathogenesis of COVID—19 Infections among Healthy Adults, Elderly and Children. *Electron J Gen Med* 2020;**17**(4).
3. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* Jul 2009;**339** b2700.
4. Aslam S, Mehra MR. COVID-19: Yet Another Coronavirus Challenge in Transplantation. *J Hear Lung Transplant [Internet]* 2020 Available fromhttps://doi.org/. doi:10.1016/j.healun.2020.03.007.
5. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med [Internet]* 2020:1–13. Available from http://www.ncbi.nlm.nih.gov/pubmed/32109013.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**(10223):497–506.
7. Analysis on 54 Mortality Cases of Coronavirus Disease 2019 in the Republic of Korea from January 19 to March 10, 2020. *J Korean Med Sci* 2020;**35**(12):1–9.
8. Lescure F-X, Bouadma L, Nguyen D, Parisey M, Wicky P-H, Behillil S, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect Dis* 2020;**2**(20):1–10.
9. Ludvigsson JF. Systematic review of COVID-19 in children show milder cases and a better prognosis than adults. *Acta Paediatr [Internet]* 2020:0–3. Available from http://www.ncbi.nlm.nih.gov/pubmed/32202343.
10. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao S-Y. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *J Thorac Oncol [Internet]* 2020. Available fromhttps://doi.org/10.1016/j.jtho.2020.02.010.
11. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;**2600**(20):1–7.
12. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China. *JAMA Oncol* 2020:25–7.
13. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet [Internet]* 2020;**395**(10229):1054–62. doi:10.1016/S0140-6736(20)30566-3.
14. Guillen E, Pineiro GJ, Revuelta I, Rodriguez D, Bodro M, Moreno A, et al. Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? *Am J Transplant [Internet]* 2020:0–3. http://www.ncbi.nlm.nih.gov/pubmed/32198834.
15. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. *Clin Infect Dis* 2020.
16. Guan W, Ph D, Liang W, Zhao Y, Med M, Liang H, et al. Comorbidity and its impact on 1,590 patients with COVID-19 in China: A Nationwide Analysis. *European Respiratory Journal* 2020 Preprint.
17. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS–CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020;**21**(3):335–7.
18. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. *Ann Oncol Off J Eur Soc Med Oncol* Mar 2020.
19. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *N Engl J Med* 2020:1–9.
20. Molloy EJ, Bearer CF. *COVID-19 in children and altered inflammatory responses*. United States: Pediatric research; 2020.
21. Brodin P. Why is COVID-19 so mild in children? *Acta Paediatr* 2020(1):0–2.
22. Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for patients with cancer. *Lancet Oncol [Internet]* 2020;**21**(4):e180. doi:10.1016/S1470-2045(20)30150-9.
23. Shrestha SS, Swerdlow DL, Borse RH, Prabhu VS, Finelli L, Atkins CY, et al. Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009-April 2010). *Clin Infect Dis* Jan 2011;**52**(Suppl 1) S75–S82.
24. Memoli MJ, Athota R, Reed S, Czajkowski L, Bristol T, Proudfoot K, et al. The natural history of influenza infection in the severely immunocompromised vs nonimmunocompromised hosts. *Clin Infect Dis* Jan 2014;**58**(2):214–24.
25. Hui DS, Azhar EI, Kim Y-J, Memish ZA, Oh M-D, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. *Lancet Infect Dis* Aug 2018;**18**(8) e217–e227.
26. Mandl JN, Ahmed R, Barreiro LB, Daszak P, Epstein JH, Virgin HW, et al. Reservoir host immune responses to emerging zoonotic viruses. *Cell* Jan 2015;**160**(1–2):20–35.
27. Mandl JN, Schneider C, Schneider DS, Baker ML. Going to Bat(s) for Studies of Disease Tolerance. *Front Immunol* 2018;**9**:2112.
28. King F. Interim Recommendations for the use of Tocilizumab in the Management of Patients who have Severe COVID-19 with Suspected Hyperinflammation Protocol: Interim Recommendations for the use of Tocilizumab in the Management of Patients who have Severe COVID-19. 2020;1–5. Available from: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/guidance/guidanceforhealthcareworkers/.
29. Hanna TP, Evans GA, Booth CM. Cancer, COVID-19 and the precautionary principle: prioritizing treatment during a global pandemic. *Nat Rev Clin Oncol.* Apr 2020.
30. Wang Z, Wang J, He J. Active and Effective Measures for the Care of Patients With Cancer During the COVID-19 Spread in China. *JAMA Oncol [Internet]* 2020 Apr 1. doi:10.1001/jamaoncol.2020.1198.
31. Al-Shamsi HO, Alhazzani W, Alhuraiji A, Coomes EA, Chemaly RF, Almuhanna M, et al. A Practical Approach to the Management of Cancer Patients During the Novel Coronavirus Disease 2019 (COVID-19) Pandemic: An International Collaborative Group. *Oncologist* Apr 2020.
32. Sinha IP, Harwood R, Semple MG, Hawcutt DB, Thursfield R, Narayan O, et al. COVID-19 infection in children. *Lancet Respir Med [Internet]* 2020;**2019**(20):2019–20. doi:10.1016/S2213-2600(20)30152-1.