Clinical Presentations and Outcomes in Transplant Patients With COVID-19: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Transplant patients are a vulnerable group due to their immunocompromised status. Understanding how COVID-19 can present in this group is clinically important. Therefore, we conduct a systematic review and meta-analysis on clinical features and management of transplant patients with COVID-19.

Methods: Five databases were searched in May 2020 to include all relevant studies reporting clinical features or outcomes of COVID-19 infection in transplant patients. Data on clinical presentation, outcomes, lab values, imaging, and drug regimen were extracted. CMA software was used for meta-analysis. Protocol was registered in PROSPERO (CRD42020189458).

Results: A total of 49 studies were finally included for analysis. Patients mainly complained from fever with event rate 74.40 % (95% CI= 69.4-78.8), cough 61.10% (95% CI= 55.8-66), and dyspnea 46.60% (95% CI= 69.4-78.8). Blood urea nitrogen 78.90% (95% CI= 54.7-92), ESR 78.10% (95% CI=52.3-92.1), and D-dimer 74.10% (95 % CI= 53-87.9) were the most elevated observed laboratory values. Ground glass opacities (GGO) were observed with event rate 68.10% (95% CI= 20.4-94.9). For treatment, immunosuppressants were used in 88.80% (95% CI= 77.6-94.8) of patients, followed by antibiotics and antiviral drugs 68.40% (95% CI= 52.4-80.9), 66.80% (95% CI = 45-83.2), respectively. Mechanical ventilation was used in 26.30% (95% CI=21-32.4) patients while 33.7% (95% CI= 20.7-49.9) intubated. Rejection occurred in 11% (95% CI= 4.4-25) of the patients. Finally, 18.20% (95% CI= 12.6-25.7) died.

Conclusion: Clinical characteristics and management in transplant COVID patients suggest the similar course in non-transplant. Fever, cough, dyspnoea, elevated blood urea nitrogen level, elevated CRP, elevated d-dimer, GGO, and consolidation were found to be the most frequent abnormalities. No direct, comparative analysis with non-transplant COVID population limited our results; however, numerous studies that examined the infected general population found similar, less augmented findings. Most of the included sample were kidney transplant patients; therefore, more studies are needed to address other types of COVID-19 infected transplant patients.

Introduction

COVID-19 is considered the worst pandemic in the last 100 years. It has spread rapidly in a few months, just after its appearance in Wuhan[1]. Immunosuppression may be attributed to various causes; organ transplantation and glucocorticoids are prevalent causes that increase risk of infections including COVID-19 [2]., literature on how being a transplant patient would affect its presentation, progression, and mortality is scarce. Recipients who receive solid organ transplants such as lung, heart, kidney, and liver are considered “high risk” for developing infection [3]. Throughout the years, improvement with graft survival and immunosuppressive agents shifted concerns of post-transplant complications towards malignancy and infection [3,4]. These transplant patients also are at risk for cardiovascular disease, which is the major cause of death and graft loss in diabetic renal transplant patients [5,6]. Hypertension and dyslipidaemia

have been reported to be common in this population as well, both of which are major risk factors for reduced renal allograft survival and cardiovascular disease [7,8]. Obesity, diabetes mellitus, bone disease, and hematologic issues have all been reported as complications found in transplant recipients [9–11]. Comparably, most of these complications can also be found in liver, heart, and lung transplant recipients in addition to the probable complications of acute or chronic transplant rejection [12,13].

Disease prevention and immunization is very important for transplant patients, but each pose their own risks to immunocompromised individuals. Lower rates of mortality have been postulated within these patients due to the blunted inflammatory response caused by immunosuppression; however, the longer the duration on immunosuppressive medications, the longer the risk of infection persists [3]. Therefore, epidemiologic exposures, i.e. this history of potential pathogen encounters and a patient's "net state of immunosuppression", must be adequately assessed to determine a patient's susceptibility to infection [3].

The COVID-19 pandemic triggered a decline in transplantation surgeries because of fear due to complications. Additionally, the heart, lungs, and kidneys have all been shown to be involved in COVID-19, which suggests that transmission from a donor is feasible; therefore, recipients and donors need to be screened before transplantation [14,15]. Additionally, the management of solid organ transplant patients requires an individualized approach, particularly with the complications of COVID-19, because the reduction in immunosuppressive therapy leads to the risk of uncontrolled infection; however, without this therapy, these patients bear the risk of transplant rejection [16,17].

Organ transplantation is thus considered to place patients at risk of fatal complications of COVID-19 due to the chronic use of immunosuppressive drugs (ISDs) and associated or coexisting comorbidities [17]. Currently, there is still limited clinical information concerning COVID-19 infected solid transplant patients, with the majority of studies reporting mainly kidney transplant patients. This systematic review and meta-analysis examined the clinical outcomes, laboratory values, CT image characteristics, and different treatment modalities for transplant patients infected with COVID-19.

Methods

Protocol registration

This systematic review was performed following the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18,19]. Detailed steps are described in **Supplementary Table 1**. A prior protocol of methods has been developed and registered with the international prospective register of systematic reviews (PROSPERO) with ID number CRD42020189458 on June 3rd, 2020.

Search strategy

We developed a search strategy to obtain all original studies reporting clinical data of transplant patients infected with COVID-19. On May 27th, 2020, we searched five electronic databases: PubMed, Web of

Science (ISI), Scopus, BioRexiv and MedRexiv using the following search term: (transplant OR transplantation OR graft) AND (recipient OR recipients OR donor OR donors OR donor) AND (SARS OR coronavirus OR nCoV OR "Cov-2" OR Cov2 OR COVID). Our search was restricted from 1st January 2020. Additional manual searches were also performed by screening references of our included studies and searching PubMed/Google Scholar for related or similar articles. More details for the search in each database and modifications on the search terms can be found in **Supplementary Table 2.**

Selection criteria

Any relevant study that reported the clinical features or outcomes of COVID-19 infection in transplantation patients were included with no restriction regarding location, gender, age, race, language, or ethnicity were included. We excluded correspondence, book chapters, abstract-only articles, conference papers, reviews, theses, posters, author responses, editorials, letters, non-extractable data, duplications, unreliable data sets, overlapping, and *in vitro* and animal studies.

Study selection

Covidence was used as a semiautomated program to conduct title/abstract screening after duplicates were removed [20]. Three independent reviewers screened full texts. Any disagreement between reviewers was resolved through discussion and consensus. If disagreement was still not resolved, a senior researcher was consulted and made the final decision.

Data extraction

Data from each study were extracted by three independent reviewers into a spreadsheet that included the following information: study characteristics such as title, first author name, publication year, country of the publication, study design, sample size, journal name; patients characteristics such as gender, age category, type of transplantation, comorbidities, and follow up duration; and outcomes such as event numbers for common signs and symptoms, vital sign categories (above normal, below normal, normal), common radiological findings, laboratory value categories (below normal, normal, elevated), positive swabs results for COVID-19 detection, hospitalization, ICU admission, mechanical ventilation, intubation, death, recovery and rejection, treatments used in terms of antivirals, antibiotics, hydroxychloroquine, immunoglobulin, anticoagulants, and steroids. Any disagreement was resolved through discussion and consensus.

Quality assessment and risk of bias

Three independent reviewers assessed quality and bias using the NIH tool for cohort, cross sectional, and case series studies. The Joanna Briggs Institute Critical Appraisal Checklist Tool was used for case reports[21,22]. Any disagreement was resolved with discussion and consensus. Scoring was one point for "YES", zero points for "NO", "cannot determine (CD)" or "not applicable (NA)". The following grading categories and score ranges were used: good, fair, and poor. In case reports: good (7-8), fair (4-6), poor (1-

3). In case series: good (7-9), fair (4-6), poor (1-3). For cross sectional studies and cohort studies: good (9-14), fair (5-8), poor (1-4).

Statistical analysis and results interpretation

Event rates and their 95% confidence intervals (CI), calculated by dividing the number of events by the number of all patients, were computed for signs, symptoms, treatments, outcomes. Subgroups based on transplantation type were formed and calculated according to available data. Studies less than or equal to 5 patients were pooled together and named as a single dataset. We used the Comprehensive Meta-analysis software (CMA) version 3.3.07 for meta-analysis (Biostat, NJ, USA). We considered heterogeneity significant if the inconsistency (I^2) of effect estimates > 50% or p-value 0.1 across studies [20]. If heterogeneity was statistically significant, we used a fixed-effects model; if not, a random-effects model was used.

Results

Systematic search and its results

A total of 446 articles were initially included from PubMed, Scopus, Web of Science, and MedRxiv databases. After removing duplicates, a total of 333 studies went through title and abstract screening. 218 articles were excluded according to exclusion criteria, leaving 115 articles for full-text screening. 46 were irrelevant to our topic, 24 non-original, Eleven contain non-extractable data and only one non-available full text. 16 articles were included from manual searches. A total of 49 articles were finally included[16,23–29,41–45,47–55,57–61,63–82]. All studies involved in our analysis. 33 studies were combined as a single case dataset with five cases or less while 16 studies were involved as them. Detailed steps are described in **Figure 1**.

Studies and participants' characteristics

Of the 49 included articles, 24 were case reports, 17 were case series, 2 were retrospective studies, 2 were cohort studies, and 4 were cross-sectional studies. 16 studies were conducted in the United States, 8 in Italy, 14 in China, 2 in Iran, 1 in Switzerland, 1 in Turkey, 1 in Korea, 1 in the Netherlands, 2 in Spain, 1 in the United Kingdom, 1 in Brazil, and 1 in Germany. Our systematic review and meta-analysis represent a total of 381 transplant patients who were infected with COVID-19. The types of transplants included liver, kidney, bone marrow, pancreas, heart, and single and bilateral lung. There was a total number of 280 males and 101 females that were represented across all studies. The age of the study subjects ranged from 13 to 80 years. The characteristics table is fully represented in **Supplementary Table 3.**

Quality Assessment

The NIH tool was used to evaluate the quality of the included studies. 42 studies showed "good" quality, 7 studies showed "fair" quality, and no studies showed "poor" quality. More details on the results of each

study are found in **Supplementary Table 3.**

Synthesis of results

Data for 381 patients were meta-analysed for pooled event rate of clinical signs and symptoms **(Figure 2)**, laboratory values **(Figure 3)**, imaging features **(Figure 4)**, and treatment modalities **(Figure 5),** patient outcomes **(Figure 6)**. Detailed data analysis results with single data set removal analysis and subgroup analysis according to the type of transplantation depending on the available data can be found in the **Supplementary Table 4.**

Clinical signs and symptoms

Figure 2 summarizes the meta-analysis for clinical signs and symptoms. Fever and cough had the highest event rates of 74.4 % (95% CI= 69.4-78.8) and 61.1% (95% CI= 55.8-66), respectively, while asymptomatic had the lowest event rate 11.30% (95% CI= 3.3-32.5). After fever and cough, the next symptom that occurred most frequently was dyspnea, which had a 46.6% event rate (95% CI= 37.2-56.3). Other symptoms that occurred had a lower event rate, with more details found in **Figure 2** and **Supplementary Table 4.**

Laboratory investigations

The laboratory findings in our study are shown in **Figure 3**. Elevated blood urea nitrogen level was the most observed at 78.90% (95% CI= 54.7-92), followed by an elevated ESR at 78.10% (95% CI= 52.3-92.1) and an elevated D-dimer at 74.10% (95% CI= 53-87.9%). More details can be seen in **Supplementary Table 4**.

Imaging features

The events rates for the radiological findings are found in **Figure 4**. The most observed feature was ground glass opacity at 68.1% (95% CI= 0.20.4-94.9), followed by consolidation at 58.4% (95% CI= 33.3-79.8) and patchy shadows at 37% (95% CI= 0.5.8-84.8). Dilated small vessels was shown in 21.8% (95% CI= 0.2-97.5) and interlobular septal thickening had the lowest event rate at 12.8% (95% CI= 0.4-83.4). More details can be seen in **Supplementary Table 4**.

Treatment modalities

Figure 5 summarizes the event rates of different medications given to COVID-19 transplant patients. The most used treatment was immunosuppressants at 88.8% (95% CI= 77.6-94.8), with antibiotics at 68.4% (9% CI= 52.4-80.9) and anti-virals at 66.8% (95% CI= 45-83.2). Immunoglobulin and hydroxychloroquine's event rate followed at 65.1% (95% CI= 30.2-88.9) and 65.0% (95% CI= 50.1-77.5), respectively. Notably, the event rate for anticoagulants was 44.9% (95% CI= 18.2-74.9). Other event rates for other types of drugs and details can be found further in **Supplementary Table 4**.

Patient clinical outcomes

The events rates of clinical outcomes for all COVID-19 infected transplant patients can be found in **Figure 6**. 77.1% (95% CI= 72-81.6) of patients hospitalized, 26.30% (95% CI=21-32.4) mechanically ventilated and 33.7% (95% CI= 20.7-49.9) intubated. Death event rate was 18.20% (95% CI=12.6-25.7) Transplant rejection occurred in four patients at 11% (95% CI= 4.4-25). Detailed data represented in **Supplementary Table 4.**

Discussion

Transplant patients face many health challenges and require careful monitoring for drug side effects and possible infections due to the immunosuppressive drugs they need to prevent organ rejection[17]. Our systematic review and meta-analysis provided evidence for the clinical outcomes, laboratory values, diagnostic imaging, and various treatment modalities used amongst transplant patients diagnosed with COVID-19.

Regarding the clinical outcomes, our findings revealed that fever (74.4%) and cough (61.1%) are the most frequently encountered symptoms. A meta-analysis done by Li *et al*. focused on the general populace in 1995 COVID-19 cases. The most common symptoms encountered in this meta-analysis were fever (88.5%) and cough (68.6%), which matches the same clinical profile of our meta-analysis[69]. The values may have slight variation due to the number of studies included in each meta-analysis; however, both studies can attest to fever and cough being the most encountered symptoms. Additionally, we found that diarrhea and dyspnea occur frequently with an event rate of 31.2% and 46.6%, respectively. The meta-analysis done by Li *et. al.* showed diarrhea to be a minor symptoms with an event rate of 4.8% and dyspnea to be considered a main clinical symptom with an event rate of 21.9%[69]. Although diarrhea could be a side effect of COVID-19, the high event rate of diarrhea from our meta-analysis could be due to the side effects of medications and polypharmacy instead of COVID-19, since post-transplant patients, compared to the general populace, commonly experience diarrhea as a symptom[70]. Expectoration (sputum production) occurs rarely with an event rate of 2.3% in our meta-analysis. Compared to the general population with an expectoration event rate of 28.2%, our findings were reduced[69]. We did not expect expectoration to be an infrequent symptom, as it seems to be common in the general populace[71].

The connection between the kidney and the lung is well established. Since most of our study involves kidney transplant patients with a single working kidney, dysfunction in that single kidney may cause these patients to be more susceptible to acidosis during an infection, leading to hyperventilation and dyspnoea as respiratory compensation [71,72]. In our meta-analysis, intubation event rate was found to be 33.7%. A systematic review and meta-analysis showed the crude prevalence of invasive mechanical ventilation in the COVID-19 general populace to be 6.79%. When compared to our population, intubation rate is significantly higher at a 26.9% difference, which supports our findings of greater respiratory distress in transplant patients[73]. Another consideration should be the similarity of symptoms between COVID-19 and influenza within vulnerable populations. Both viruses have been shown to present with similar symptoms like fever, diarrhoea, myalgia, malaise, and dyspnoea. The initial outbreak of COVID-19

occurred during a period where there were high rates of respiratory viruses such as respiratory syncytial virus, influenza, and many others. Vaccines such as the influenza vaccine are useful in reducing the confusion between symptoms caused by COVID-19 and other similar respiratory viruses[74]. Obtaining knowledge of the vaccination history as well as prior infection history of our patients in our study may help better explain some of our findings[25]. Obtaining prior knowledge is particularly important since the aforementioned respiratory viruses, in addition to the respiratory syncytial virus, parainfluenza virus, and rhinovirus, are becoming more recognized as major causes of respiratory illnesses in patients after receiving a single organ transplant[26].

Additionally, comorbid conditions like diabetes and heart failure in transplant patients are common and may further complicate the COVID-19 infection. For instance, in a study that assessed comorbid conditions in kidney transplant patients, diabetes was found in 30.3% of patients and heart failure was found in 11.9% [74]. Another study that explored comorbid conditions in lung transplant patients showed that, out of 223 people, 19.7% had diabetes and 9% had heart failure. These conditions seem to be common in transplant patients, compared to the 9.7% who had diabetes and 8.4% who had cardiovascular disease as seen in a systematic review and meta-analysis reviewing commodities in the general COVID-19 infected population; therefore, increased prevalence of certain comorbidities could also affect the clinical outcome of transplant patients[25,29].

Regarding the laboratory values found within our meta-analysis, abnormalities were typical for all patients hospitalized with COVID-19 and not just transplant patients. Liver injury secondary to COVID-19, like prolonged prothrombin time, elevated aminotransferases, and hypoproteinemia, have been reported by numerous studies and are thought to be due to direct liver damage from the virus itself, drug hepatotoxicity, and immune-mediated inflammation[26]. COVID-19 is associated with immunosuppression, causing a depression in CD4+ and CD8+ lymphocytes and leading to lymphopenia. Elevated ESR, CRP, and D-Dimer reflect an inflammatory state typical of a COVID-19 infection, with an increase of LDH reflecting systematic damage in the body [23]. There is a parallel response in the inflammatory mediators in COVID-19 and the disease severity. The laboratory findings in our meta-analysis show that 59.3% of our patients had elevated IL-6 markers. IL-6 is an interleukin that stimulates acute phase responses, immune reactions, and haematopoiesis as a response to tissue injury and infections. An increasing rise in this marker may be an indication of the severity of COVID-19[23]. According to the case report done by Hammami *et al.*, the timing of the administration of particular immunosuppressive therapy may help reverse the progression from mild to severe inflammatory response associated with COVID-19[23].

In reference to the diagnostic imaging reported by our meta-analysis, our study showed that consolidation had an event rate of 58.4% and was the 2nd most frequent characteristic. When compared to a systematic review of different imaging features in 919 COVID-19 patients, only 10 studies reported consolidation; thus, demonstrating the lease percentage of cases at 31.8 [75]. Other than this discrepancy, our findings generally agree that COVID-19 images for transplant patients are often bilateral with consolidation and ground glass opacity, with pleural effusion being the least prevalent feature [24]. The

severity of COVID-19 is believed to primarily be influenced by the inflammatory response that was discussed previously. Patients who present with COVID-19 pneumonia with progression to acute respiratory distress syndrome therefore have a higher inflammation-related index. The consolidation and characteristic pleural effusion represent the pulmonary inflammatory response caused by the elevated IL-6 in the blood[23].

We found that 11% of the total patients in our study experienced transplant rejection. Rejection varied from minimal cellular rejection to acute organ rejection and deterioration in donor organ function. According to the data available, there is no exact relationship between change in the regimen of treatment and rejection, although it was reported that respiratory viral infection may lead to rejection [28]. Acute organ rejection was witnessed in four patients; however, the rejections occurred before COVID-19 infection, which suggests that acute rejection secondary to COVID-19 is likely a minimal feature[26].

We found the death rate of COVID-19 transplant patients to be 18.2%. In a meta-analysis and systematic review done by Jutzeler *et. al* which measured COVID-19 in the general population, the death rate was 7.97%[73]. The death rate found in the transplant patients within our meta-analysis is almost double this value. This does not come as a surprise when analysing potential causes of death in solid organ transplant patients infected with COVID-19 within similar studies. Our findings agree with the 2007 study done by Fishman *et.al.* which found that transplant patients using immunosuppressants are susceptible to serious infection and other complications[3]. However, our meta-analysis shows that most patients were not put on anti-coagulation, which had an event ratio of 44.9%. Our analysis did not include causes of death; however, we can surmise from the anti-coagulation event rate that lack of anticoagulation could have elevated the fatality rate due to complications arising from venous thromboembolism for all types of COVID-19 infected transplant patients. According to Ahmed *et al*., targeting COVID-19 without reducing the risk for thrombosis is rudimentary, since the formation of microthrombi is common in these patients. These microthrombi have been shown to form in the lung vasculature and alter lung perfusion, thus leading to hypoxemia that can ultimately lead to death[76,77].

Finally, in reference to various treatment methods presented in our meta-analysis, the most common treatment found in organ transplant patients diagnosed with COVID-19 are immunosuppressants[23,24,27]. Jutzeler *et al*. corticosteroids are commonly administered to hospitalized patients with severe disease despite the controversy of their benefit [73]. From the studies included, hydroxychloroquine was the second most frequently administered drug, followed by antibiotics and antivirals [78]. According to In our meta-analysis, we observed high percentages of withdrawal or decrease in dosage of such immunosuppressant drugs, with kidney transplant patients having the highest event rates of withdrawal at 63% and liver transplant patients with the highest event rates of dosage decrease at 75.0%. It is possible that patients began experiencing side-effects of immunosuppressive therapy or acquired comorbidities such as hypertension, kidney failure, chronic myelosuppression, or others, which may explain the high event rates [27]. Another possible explanation is that patients began to improve to a point that did not warrant the dosages of immunosuppressant drugs that were initially prescribed.

Limitations

Our meta-analysis did not analyse the clinical complications in each study, such as myocarditis, arrhythmias, heart attacks, strokes, or bacterial co-infection. The number of lung transplant, heart transplant, and liver transplant patients infected by COVID-19 is limited in this study, as most patients in this study are kidney transplant patients. Therefore, the results from the meta-analysis must be taken carefully for non-kidney transplant patients. This study did not meta-analyse the difference between transplant and non-transplant patients. Most of the included studies are case reports/series with short follow up. This increases the need for a randomized control trial comparing the outcomes between the two populations.

Conclusion

In conclusion, fever, cough, dyspnoea, elevated blood urea nitrogen level, elevated CRP, elevated d-dimer, GGO, and consolidation are the most prevalent abnormalities in transplant patients with COVID-19. These abnormalities are augmented in transplant patients; however, they can also be found within the general population. Since kidney transplant patients represented most of the included sample, more studies are needed to address other types of COVID-19 infected transplant patients, the efficacy of different treatment modalities, and longer follow up periods.

Declarations

- Ethics approval and consent to participate - Not applicable for Systematic Review
- Consent for publication - Yes all authors consent to publication and have seen this final version of the manuscript

Data Availability Statement

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Availability of data and materials: Available to Publish, not published before

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Conflict of interest/Competing Interests

The authors had no conflict of interest to conduct this study

Author Contributions

JS was responsible for the idea under supervision of NTH. KSA, NA, FEY and EMK organized tasks, made tables and figures under supervision of NTH. Data analysis was done by KSA, NA and HAS. EMM revised it. All authors KSA, JSA, NA, FEY, EMM, EMK, HAS, YEE, NKA, RMG, MAA, NL, MA, ZAM, SAD, SNKD, NQP, AB, JV, NTH contributed to the manuscript writing, manuscript proofreading, revision and approval of the final version.

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Figures

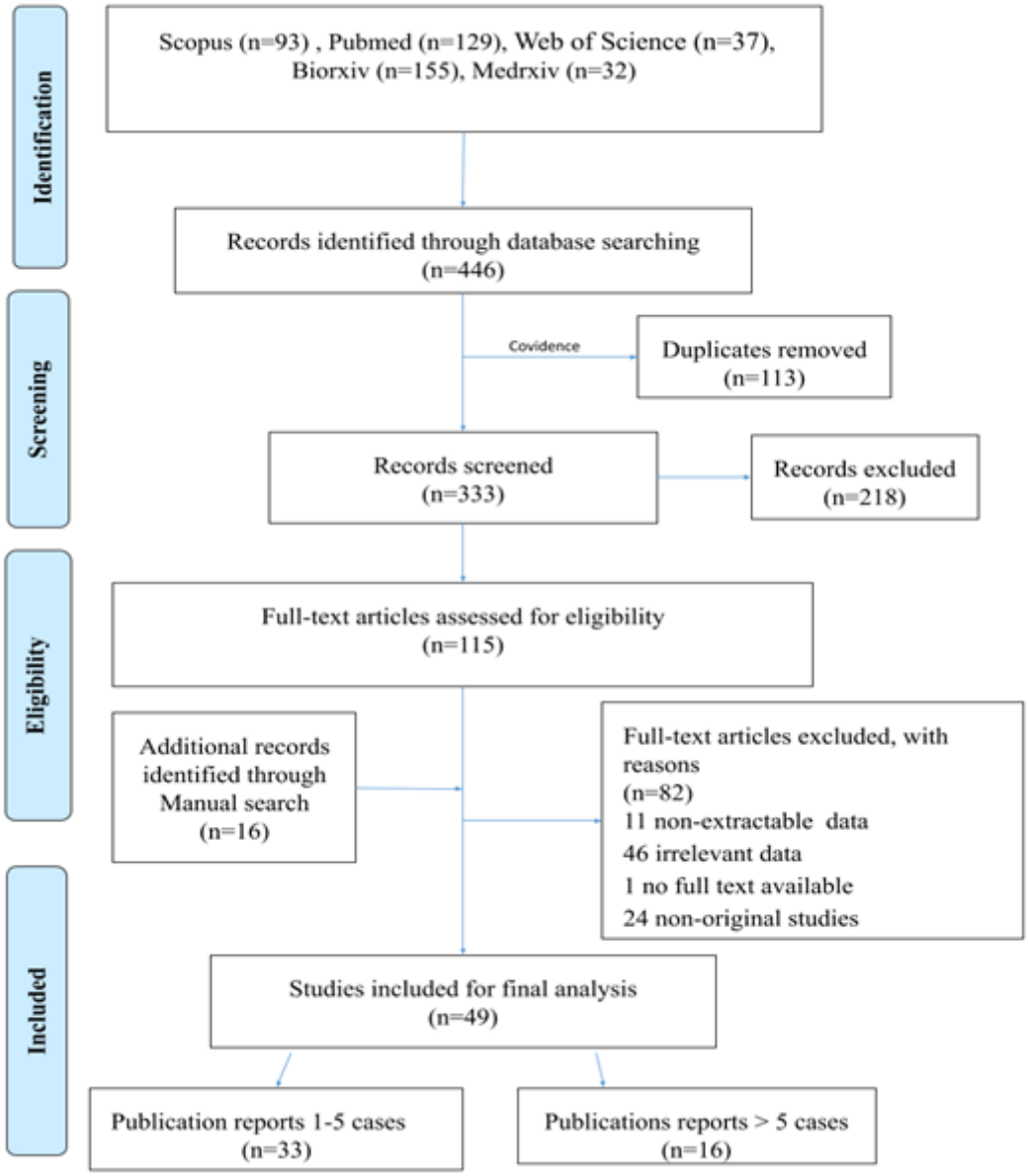

Figure 1

PRISMA flow diagram of study screening and selection.

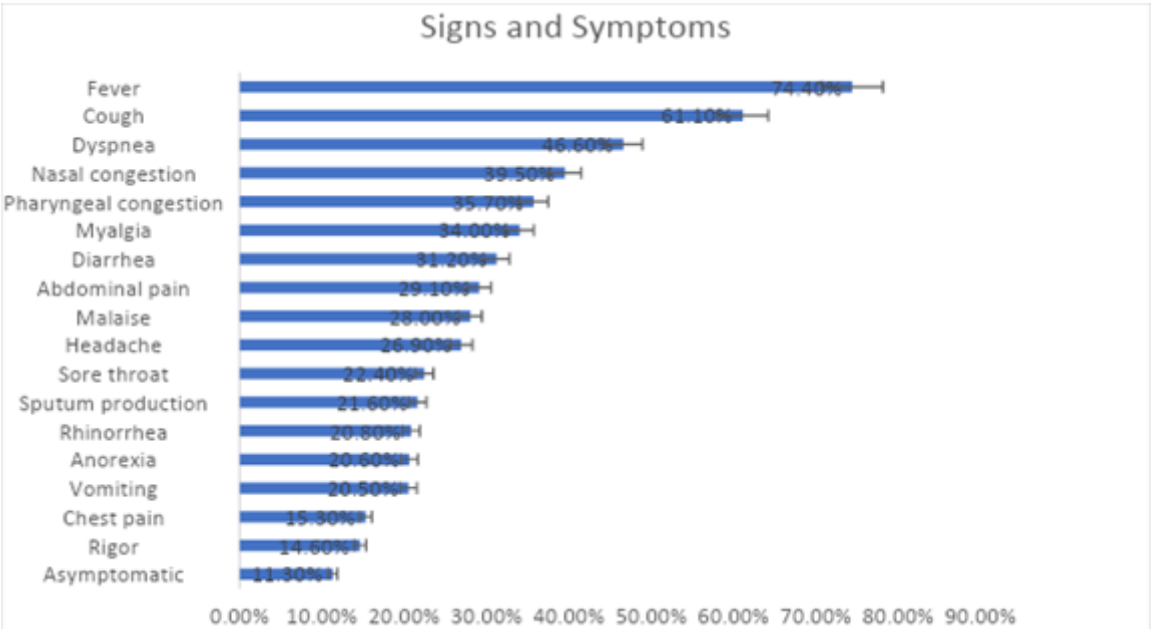

Figure 2

Event rates for signs and symptoms.

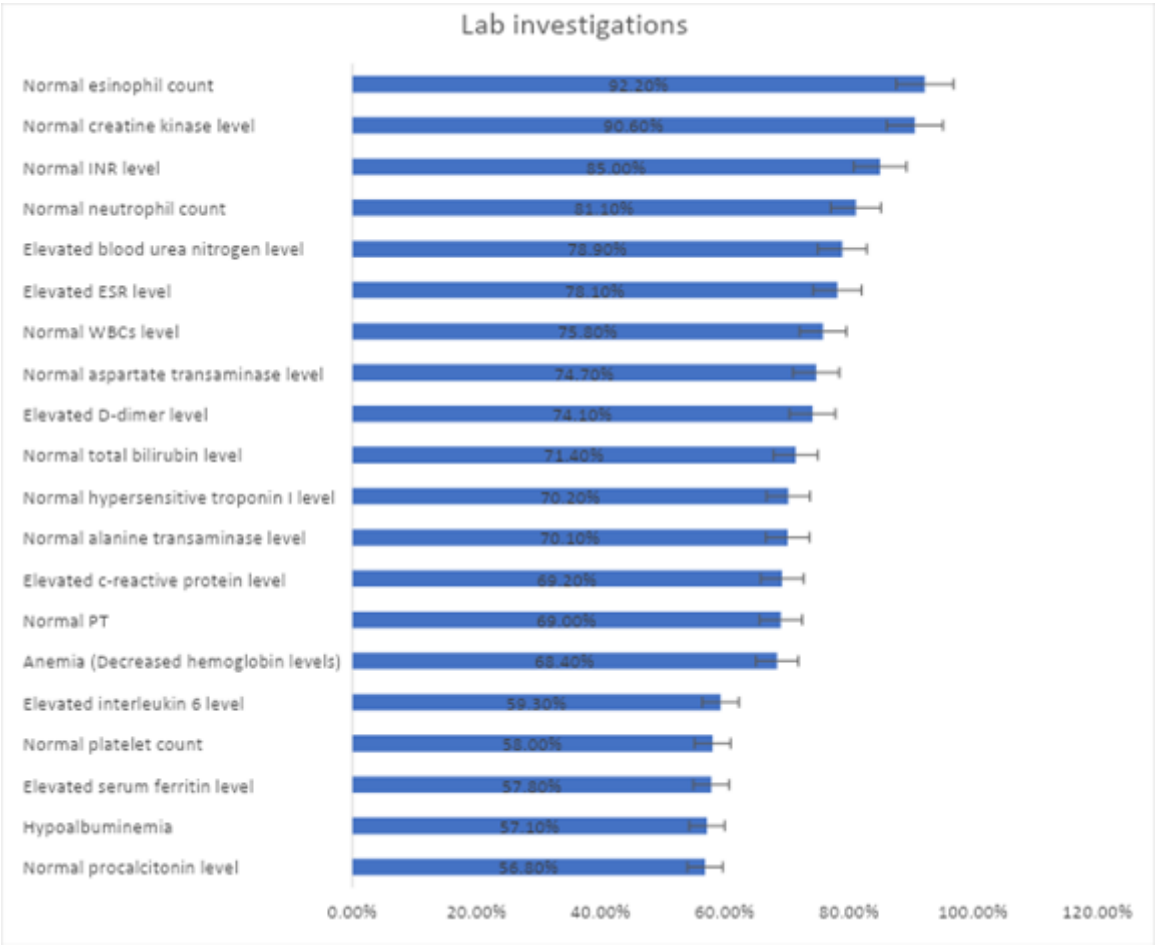

Figure 3

Lab investigation in transplant patients.

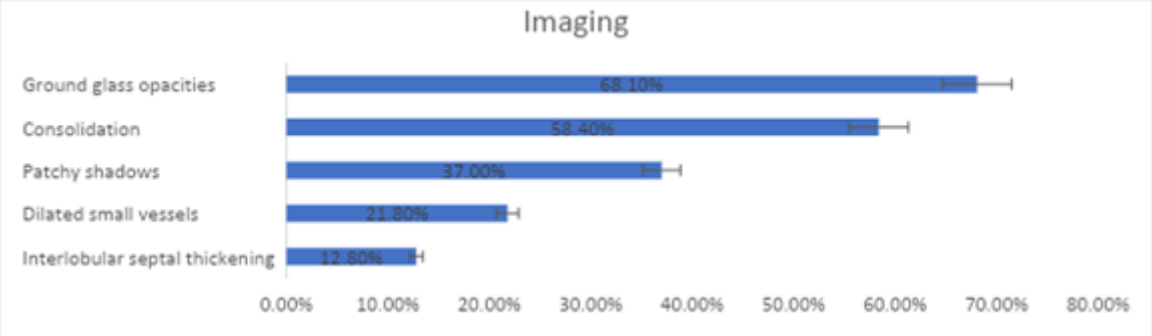

Figure 4

Event rates of image features in transplant patients.

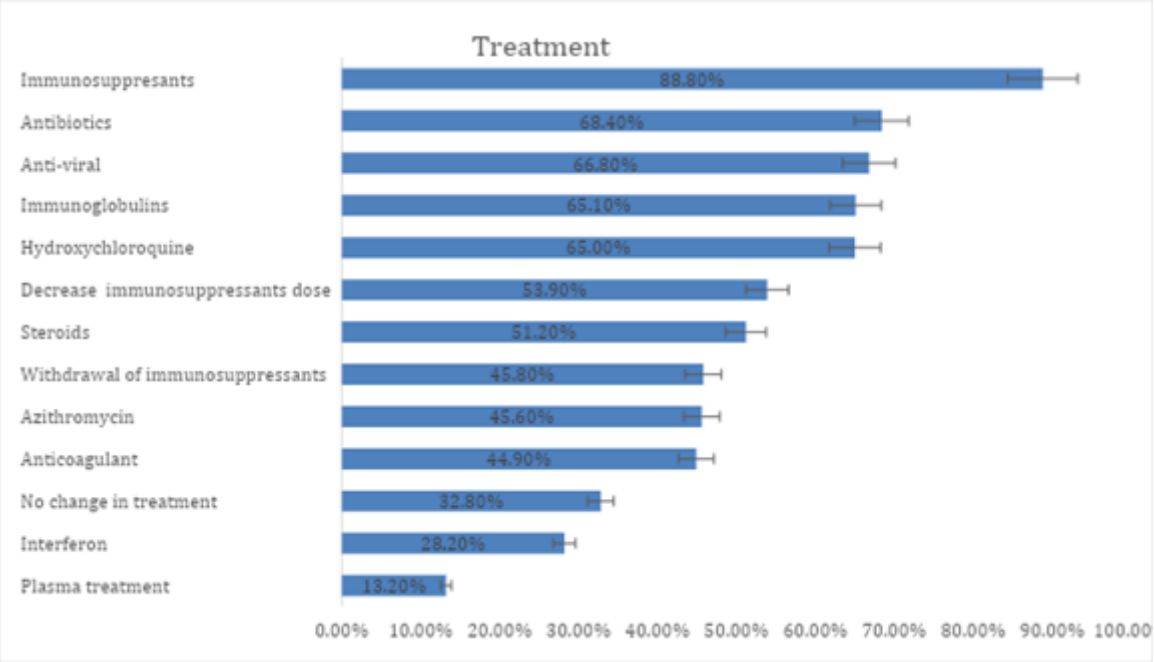

Figure 5

Event rates of treatments used in transplant patients.

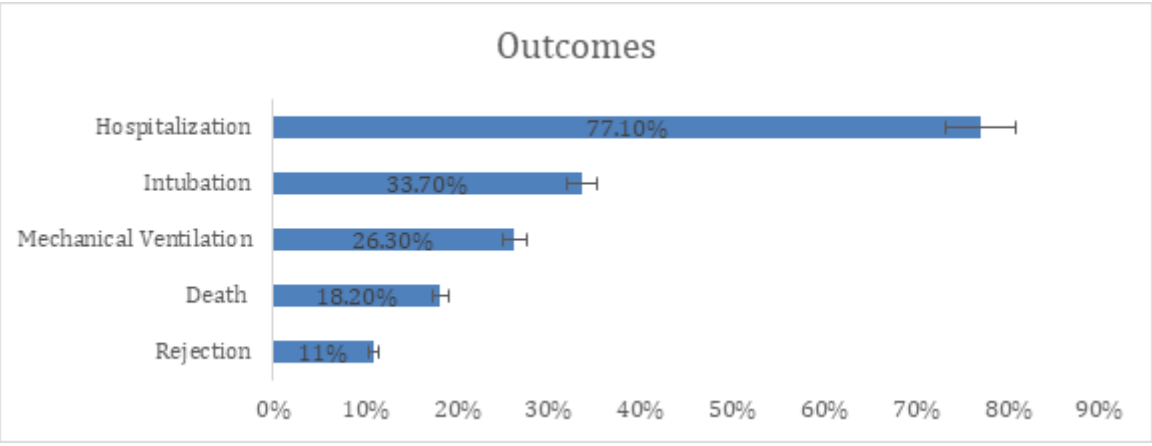

Figure 6

Clinical outcomes in transplant patients.

Supplementary Files

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