Research Article

Liver transplantation without pneumocytsis jirovecii prophylaxis - Single center experience
Running title: Infection in liver transplantation

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Abbreviations
Pneumocystis jirovecii (PJ); Solid organ transplant (SOT); Pneumocystis jirovecii pneumonia (PJP); Liver transplant (LTx); Model for end-stage liver disease (MELD); Orthotopic liver transplantation (OLT); Trimethoprim-sulfamethoxazole (TMP-SMX); Cytomegalovirus (CMV); Acute cellular rejection (ACR); Living donor liver transplantation (LDLT); Deceased donor liver transplantation (DDLT); Bronchoalveolar lavage (BAL)

Abstract

Background and Aim: Pneumocystis jirovecii (PJ) can be seen in solid organ transplant (SOT) recipients. Despite guidelines recommending PJP prophylaxis for 6–12 months post-transplantation, the necessity for liver transplant patients remains controversial, with conflicting evidence on PJP rates. This study examined PJP occurrence in 242 liver transplant patients at a single center who received no PJP prophylaxis.

Material and Methods: A retrospective study examined the clinical and microbiological data of 242 liver transplant (LTx) patients to evaluate PJP incidence within one year post-transplant. PJP was diagnosed microbiologically and/or radiologically in cases of clinical suspicion, without systematic screening. The study investigated PJP infection risk factors reported previously, including cytomegalovirus (CMV) infection, bolus steroid therapy, age >65, prolonged neutropenia, and anti-thymocyte globulin (ATG) usage.

Results: The study involved 242 liver transplant recipients, with an average age of 56 years, predominantly male (71%), and a mean Model for End-Stage Liver Disease (MELD) score of 16. No PJP cases were reported. Among PJP risk factors, none had prolonged neutropenia, though two developed CMV infection. Empirical steroid bolus treatment for suspected acute cellular rejection was given to 62 patients (26%). The cohort included 22 (9%) individuals over 65 years old, and none received ATG.

Conclusion: This pioneering study examines a substantial living liver donor transplantation (LDLT) cohort without PJP prophylaxis, suggesting it may be unnecessary in centers with low immunosuppression and a low percentage of risk factors. Prospective studies are essential to establish targeted prophylactic approaches due to variations in PJP incidence across centers.

Keywords: Immunosupression; liver transplantation; prophylaxis; pneumocytis jirovecii pneumonia.

Introduction

Pneumocystis jirovecii (PJ), formerly referred to as Pneumocystis carinii, is a widespread opportunistic organism that primarily affects immunocompromised individuals, such as those who have received solid organ transplants (SOT). The majority of opportunistic infections emerge within 1 to 6 months following orthotopic liver transplantation (OLT), coinciding with the period of higher-intensity immunosuppression.[1] According to established protocols, SOT recipients are typically recommended to undergo Pneumocystis jirovecii pneumonia (PJP) prophylaxis during the initial 6–12 months post-transplantation.[2-6]

Trimethoprim-sulfamethoxazole (TMP-SMX) is considered the optimal preventive treatment for SOT. Although PJP prophylaxis is advocated for SOT recipients in guidelines, reviews, and population-based studies, its necessity for liver transplant patients remains controversial.[7-9] While in the 1980s the incidence of PJP was high, recent studies have shown a low PJP incidence in LT recipients without prophylaxis.[10-14]

On the other hand, other single-center studies show an increased risk of PJP that warrants prophylaxis.[14-16] Although there is some evidence indicating no significant increase in the incidence of PJP without preventive measures, a comprehensive population-based study revealed an elevated risk of PJP among transplant recipients compared to the general population, persisting even after two years post-transplantation.[9]

The aim of this study is to examine the occurrence of PJP in a cohort of 242 liver transplant patients without PJP prophylaxis at a single center.

Material and Methods

Study Population

A retrospective study examined the clinical and microbiological data of 248 consecutive liver transplant (LTx) patients. Data were gathered retrospectively from patient records. Patients were monitored monthly for the first three months, and subsequently every three months for the first year. International patients who could not attend our centers had follow-up appointments via televisits with the same schedule. Any medical treatment outside our center was consulted with our team.

The analysis excluded six patients who did not survive beyond five days post-LTx. One died due to intraoperative cardiac arrest, two due to primary non-graft function, two due to multi-organ failure, and one due to intracranial hemorrhage. No postmortem analysis for PJ was conducted. Two patients who received second transplants at 150 and 1,071 days due to primary disease recurrence were evaluated as new index

transplants. The study omitted two patients who underwent combined kidney-liver transplantation, as they received PJP prophylaxis per protocol in our kidney transplant patients. Consequently, the final analysis included a total of 242 LTs (Fig. 1). Table 1 presents the recipients' demographic and perioperative data. All surviving patients were monitored for at least one year.

Living donors provided right liver grafts for 225 of the 242 LT patients (93%). The piggy-back technique was used in all cases, including cadaveric transplants. An infectious disease expert, collaborating with a multidisciplinary medical group, managed the treatment of liver transplant patients with suspected or confirmed infections. Patients received piperacillin-tazobactam as prophylaxis during the perioperative phase. Antifungal and anti-PJP prophylaxis were not administered. Instead, patients were prescribed nystatin 50,000 U thrice daily for the initial three months post-transplantation to prevent mucosal candidiasis.

When infections occurred, broad-spectrum antimicrobials were empirically administered after obtaining appropriate cultures. Treatment was adjusted based on the identified pathogens and antibiotic susceptibility. Patients underwent a three-month course of valganciclovir for anti-cytomegalovirus (CMV) prophylaxis, beginning within the first week after liver transplantation, and were monitored for potential infectious complications.

If a patient had pneumonia with suggestive radiographic findings, PJP was clinically suspected. Definitive diagnosis of PJP was established by identification of the organism in sputum samples (when accessible) or bronchoalveolar lavage (BAL) specimens either by Giemsa staining, fluorescent antibody staining, or polymerase chain reaction assays. Analysis of BAL was performed by a pathologist together with an infectious disease specialist. No lung biopsies were taken. When definitive diagnosis could not be made in patients with highly suggestive clinical and radiological findings, a presumptive diagnosis was made, and the existing empirical treatment was continued or newly started. No systematic screening for PJ was conducted using any tests.

Additional outcome measures included the frequency of severe acute rejection that did not resolve spontaneously and the incidence of active CMV infection or disease. Risk factors previously defined by guidelines from the American Society of Transplantation Infectious Diseases Community of Practice were evaluated in our cohort.[5] All protocols were performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. The Gazi University Ethical Commission approved this study (31.01.2025/E.1157653).

Immunosuppressive Protocol

The immunosuppression protocol employed a triple regimen of low-dose tacrolimus. Initially, tacrolimus was given at 0.05 mg/kg/day, divided into two doses, with target whole-blood trough levels of 8–10 ng/mL during the first three months post-transplantation, and 6–8 ng/mL subsequently. Mycophenolate mofetil was initiated within 24 hours of transplant at 1.5 g/day, administered in two doses.

The corticosteroid regimen began with 100 mg/day methylprednisolone on the first day, gradually tapered to a maintenance dose of 15 mg/day by the tenth day and discontinued after three months, except for cases with autoimmune liver disease as the etiology of cirrhosis. Acute cellular rejection episodes were managed with intravenous bolus corticosteroid therapy using 2 g methylprednisolone.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version 26; IBM Corporation, Armonk, NY, USA). Categorical variables were presented as numbers and percentages, whereas normally distributed variables were expressed as the mean ± standard deviation. For non-parametrically distributed variables, the median (minimum–maximum) and interquartile range (25%–75%) were used.

Results

Demographic Variables

In our patient group, the average age was 56 years, with males comprising 71% of the participants. The mean MELD score was 16. Among the

Incidence of Opportunistic Infections

Fifteen patients underwent BAL due to suspected PJP, while sputum samples were analyzed for 20 patients, and no lung biopsies were performed. There was not a single case with a definitive or presumptive diagnosis of PJP in the cohort.

Two cases of CMV infection were encountered. A total of 14 fungal infections were recorded, seven of which were classified as invasive fungal infections. Antifungal and antimicrobial therapy within 100 days post-transplant was documented. In the first 100 days following surgery, 42 patients (17%) were administered empirical antifungal treatment alongside antibiotics due to suspected fungal infections. Once a fungal infection was ruled out, antifungal medication was discontinued. Fifteen patients were treated solely with antimicrobial therapy due to bacterial infections.

Risk Factors for PJP

The American Society of Transplantation Infectious Diseases Community of Practice identifies several risk factors for PJP, including prolonged neutropenia, CMV infection, empirical bolus steroid therapy, age >65, and administration of ATG. Neutropenia was defined as <0.5 □ 10^9/L.

During the evaluation of defined PJP risk factors, no patients experienced prolonged neutropenia, although two individuals developed CMV infection. A total of 62 patients were administered empirical steroid bolus therapy due to suspected acute cellular rejection (ACR). Given that the majority of transplants were living donor liver transplants (LDLT), liver biopsies are frequently avoided in suspected ACR cases to minimize potential risks to the graft. Only two patients underwent liver biopsies, which confirmed ACR. All patients responded positively to empirical steroid treatment. The patient cohort included 22 (9%) individuals over 65 years old. No patient received ATG.

Discussion

PJP is a devastating condition with a high mortality rate among immunocompromised patients. Hence, guidelines recommend PJP prophylaxis in SOT patients.[5,17]

Despite these recommendations, various medical facilities worldwide implement total prophylaxis, selective prophylaxis, or none. A multicenter survey endorsed by the European Liver and Intestine Transplant Association found large variations in antibiotic and antifungal prophylaxis across transplant centers.[18]

According to the protocol at our center, no preventive treatment was administered to patients at risk for PJP. No cases of PJP infection were observed during the first year of follow-up. This finding aligns with other studies showing a low rate or no incidence of PJP infection without prophylaxis or with short-term prophylaxis for three months.[15-17,19,20]

A systematic review and statistical analysis of randomized controlled trials suggest that adult patients should be considered for PJP preventive measures when their risk exceeds 3.5%.[8] In contrast, a recent population-based study comparing 10,530 SOT recipients, including 4,281 LT recipients, with non-SOT individuals using propensity score matching found that SOT recipients had a greater risk of developing PJP, which could manifest at any time post-transplantation. SOT recipients with coexisting HIV infection, hematologic malignancies, or vasculitis have an increased risk of PJP.[9]

During the early years of liver transplantation, more intensive protocols adopted from kidney transplant practices necessitated PJP prophylaxis. Over the past ten years, less aggressive immunosuppressive strategies have been adopted, raising questions about the necessity of such preventive measures. Some centers still utilize rigorous immunosuppressive approaches, with ATG administered to 20% of patients and triple immunosuppressive therapy administered to 60%.[21]

The absence of PJP cases in our center may be attributed to our minimal immunosuppressive protocol. Additionally, PJP infection risk factors were scarce; only two patients had CMV infection, none experienced prolonged neutropenia, and none received ATG. Empirical bolus steroid therapy was administered to only 62/242 (25%) patients, while 22/242 (9%) were >65 years old (Table 2). The low prevalence or absence of PJP infection risk factors likely contributed to the low incidence of PJP in our cohort, consistent with previous studies showing a correlation between these risk factors and PJP development.[22,23]

Research and guidelines on invasive fungal infection risk identify biliary leaks and high MELD scores as contributing factors.[24,25] Most studies reporting low PJP incidence without prophylaxis did not include MELD scores in their analyses. Our center's median MELD score of 16 is comparatively low for many Western counterparts. Our experience with living donor liver transplantation (LDLT) and elective procedures could be the primary reason for fewer complications and reduced post-intensive care unit stay. In contrast, Western centers predominantly perform deceased donor liver transplantation (DDLT) with high MELD scores, which could explain the higher risk of PJP infection.

Following transplantation, drug toxicity often causes liver enzyme elevation, with antibiotics being the main culprit in most cases.[26] TMP-SMX is known to induce various side effects, including bone marrow suppression, elevated creatinine, hyperkalemia, rash, Stevens-Johnson syndrome, and liver enzyme elevation.[27] Consequently, it is advisable to minimize unnecessary antibiotic use in these patients.

Globally, conflicting results regarding anti-PJP prophylaxis exist owing to variations in immunosuppressive protocols, geographical differences in PJP incidence, risk factor prevalence, LDLT versus DDLT, and potentially MELD scores. Therefore, prospective multicenter studies are essential to avoid unnecessary prophylaxis and to implement a targeted, selective approach.

The main drawbacks of our study include its retrospective nature, the limited one-year follow-up period, and the inability to define PJP risk factors due to the absence of PJP infection cases.

Conclusion

This study represents the first comprehensive analysis of a major LDLT cohort without PJP prophylaxis. Our findings indicate that anti-PJP prophylaxis may not be essential in centers incorporating low-intensity immunosuppressive protocols with a low incidence of PJP risk factors. The persistence of variations in PJP incidence among centers necessitates prospective studies to develop targeted prophylactic strategies globally.

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Table 1. Patient basic characteristics

Characteristic	Evaluable subjects (n=242)
Age, mean (std)	56 ± 11*
Male, n (%)	171 (71 %)
MELD†, mean (std)	16 (6-40)**
Etiology, n (%)	
Non-tumor	164 (68 %)
With tumor	78 (32 %)
HCC	74 (31 %)
Perioperative variables	
CIT, min	80 (40-632)**
Op time, min	501 (185-950)**
PRBC, units	3.1 ±3.1
ICU stay, days	1 (1-30)**
ICU stay >48 h, n (%)	66 (27 %)
BL n(%)	40 (17%)
LDLT n(%)	223 (92%)

*(Mean±standard deviation) **(Median 25%-75%)

MELD: Model of end stage liver disease; †: biologic MELD; HCC: Hepatocellular carcinoma; CIT: Cold ischemia time; PRBC: Packed red blood cells; ICU: Intensive care unit; BL: Biliary leak; LDLT: Living donor liver transplantations.

Table 2. Number of patients having risk factors for PJP infection

Risk factors	n (%)
Prolonged neutropenia	0 (0%)
CMV infection	2 (1 %)
Empiric bolus corticosteroid therapy	62 (26%)
Advanced age >65	22 (9%)

ATG	0 (0%)

ATG: Antithymocyte globulin; CMV: Cytomegalovirus infection.

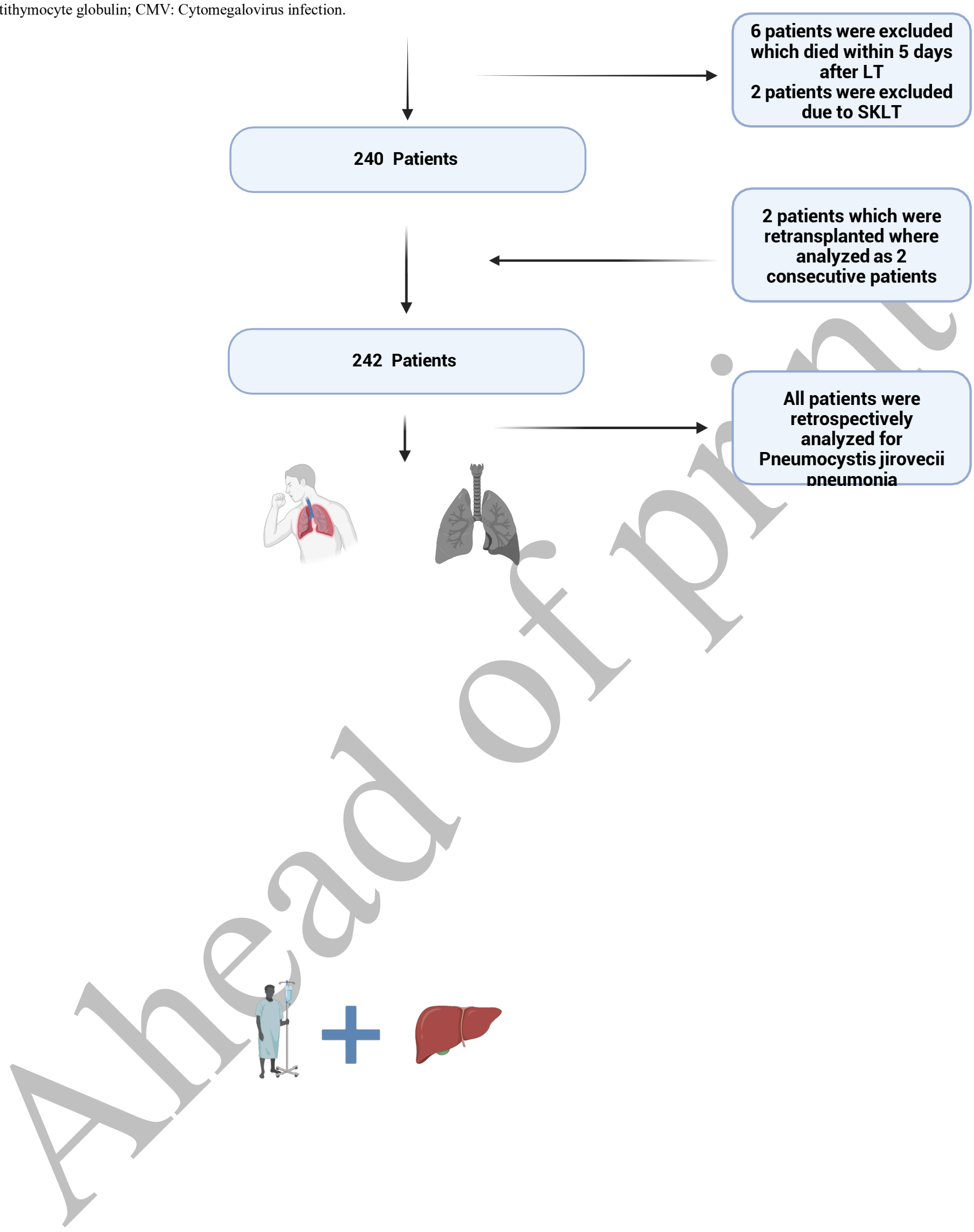

Figure 1. Flow chart of the study

SKLT: Simultaneous kidney-liver transplantation**.**