Evaluation of liver transplantation services in Kazakhstan: 2012-2023

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Abstract

There is a scarcity of publications evaluating the performance of the national liver transplantation (LTx) program in Kazakhstan. To address this gap, this study aimed to analyze historical trends in LTx surgeries and liver transplant centers from inception (2012) to the present (2023). Additionally, the study analyzes the national cohort of patients awaiting LTx, examining their survival, and assesses the epidemiology of common liver disorders indicating LTx. A survival analysis of patients awaiting LTx but not receiving it was conducted using life tables and Kaplan-Meier methods. Time series analysis was applied to examine historical trends of LTx, liver transplant centers per million populations (pmp), and selected types of viral hepatitis and liver cirrhosis per 100,000 populations, projecting future developments until 2030. The overall pmp rate of LTx ranged from 0.35 to 3.77, with LTx from living donors surpassing those from deceased donors multiple times. The pmp rates of liver transplant centers ranged from 0.06 to 0.40. A total of 474 patients underwent LTx, while another 364 patients were on the waiting list but did not receive transplantation. The 30-day cumulative survival on the waiting list was 87.0Without targeted interventions, the pmp rates of LTx and liver transplant centers are expected to remain stable, contributing to the backlog of unoperated patients awaiting transplantation.

Keywords: liver transplantation, fibrosis and cirrhosis, viral hepatitis, survival, time series, Kazakhstan.

1. Introduction

Liver failure, characterized by the inability of the liver to perform its metabolic and synthetic functions adequately, poses a growing public health challenge. It manifests as acute or chronic, triggered by various liver diseases such as viral and autoimmune hepatitis, cirrhosis, hepatocellular carcinoma, metabolic liver diseases, among others [1]. Acute hepatic failure progresses rapidly within less than 12 weeks, with drug-induced liver injury being the primary cause in developed nations, while viral hepatitis prevails in developing countries [2]. Chronic liver failure, lasting more than 6 months, represents a progressive deterioration of liver functions commonly attributed to liver fibrosis and cirrhosis, the advanced stages of liver disease [3]. Despite recent strides in managing viral hepatitis through widespread vaccination against hepatitis B and improved hepatitis C treatment, cirrhosis's prevalence is on the rise, ranking as the 11th leading cause of death and 15th leading cause of morbidity in 2016 [4].

Treatment for both acute and chronic liver failure focuses on addressing the underlying cause and managing associated complications [1]. Liver Transplantation (LTx) stands as the gold standard of care for patients with acute and chronic end-stage liver failure, especially when medical therapy proves ineffective [5]. Indications for LTx include hepatic encephalopathy, bleeding varices, or ascites, and decisions are based on a comprehensive examination. Various scoring systems integrating biochemical tests with patients' clinical presentations have been proposed to select suitable candidates for LTx [6, 7]. Despite advancements in LTx techniques, a successful surgery requires a multidisciplinary approach involving an interprofessional team and substantial financial resources [8].

Typically, two sources of donors are used for LTx: living and deceased. Deceased donor transplants constitute the majority in the Western world, exceeding 90 %, while in many Asian countries, there is a greater reliance on living donors, contributing to 24 % of global LTx in 2022 [9]. The Global Observatory on Donation and Transplantation (GODT) reported 37,436 LTx surgeries in 2022, reflecting an 8 % increase from 2021 [10]. Despite this increase, the demand for LTx far surpasses the supply, resulting in patients on waiting lists either succumbing to their conditions without receiving transplants or becoming unsuitable candidates for LTx [9].

Kazakhstan, a former Soviet state in Central Asia, initiated LTx activities in 2012. Like other Asian countries, living donor transplantations are more prevalent than cadaveric LTx, contributing to one of the lowest LTx rates globally [10]. However, there is a dearth of publications evaluating the performance of the national LTx program. Existing reports focus on single-center activities [11, 12, 13], lacking a comprehensive evaluation essential for enhancing the national LTx program to meet the needs of the population. Therefore, this study aims to evaluate the national LTx service over a 12-year period (2012-2023). It specifically seeks to analyze historical trends in living donor

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and deceased donor LTx surgeries and LTx centers, projecting future developments until 2030. Additionally, the study aims to analyze the national cohort of patients awaiting LTx, examine their survival, and assess the epidemiology of common liver disorders indicating LTx. Future projections until 2030 will be made to anticipate the demand for LTx.

2. Materials and methods

2.1. Data sources

Various data sources were utilized to conduct this study. The primary data source was the database maintained by the Republican Center for Coordination of Transplantation and High-Tech Services under the Ministry of Health (MoH) of Kazakhstan, hereafter referred to as the Transplantation Coordination Center. This center serves as the main coordination body in the country, collecting information on potential donors and recipients and overseeing transplantation activities. As part of its responsibilities, the Transplantation Coordination Center manages the waiting list of patients awaiting LTx, initiated in 2012 concurrent with the introduction of liver transplantations in Kazakhstan.

From this database, we extracted information on patients awaiting LTx but who never received it. The extracted data included the date of registration on the waiting list, current status (alive vs. deceased), and date of death (if applicable). For patients still alive at the time of data extraction, December 12, 2023, was considered the end of the follow-up period. Additional anonymized information extracted from the waiting list encompassed patient details such as age, sex, rhesus D antigen (RhD), and blood group. Data obtained from the Transplantation Coordination Center also included the number of living and cadaveric liver transplants in Kazakhstan, categorized by the year of surgery, as well as the count of LTx centers by year, and the number of LTx surgeries performed in each center, also by year. The timeline covered by these data spans from January 1, 2012, to December 12, 2023.

To complement findings on the number of patients awaiting LTx, official statistics on patients with liver diseases qualifying for LTx, as outlined in the national standard of care on LTx ([14], were obtained from the Electronic register of dispensary patients of the MoH. This electronic register encompasses information on all patients registered by healthcare facilities in Kazakhstan. Extracted data included the annual numbers of patients presenting with selected types of viral hepatitis and liver fibrosis and cirrhosis at outpatient healthcare facilities in Kazakhstan. Specifically, we addressed the following the International Classification of Disease 10th revision (ICD-10) codes for acute and chronic viral hepatitis: B15.0 (Hepatitis A with hepatic coma), B16.0 (Acute hepatitis B with delta-agent (coinfection) with hepatic coma), B18.0 (Chronic viral hepatitis B with delta-agent), B18.1 (Chronic viral hepatitis B without delta-agent), B18.2 (Chronic viral hepatitis C), B18.8 (Other chronic viral hepatitis), and B18.9 (Chronic viral hepatitis, unspecified). Regarding liver fibrosis and cirrhosis, the annual number of patients with the following ICD-10 codes was extracted: K74.0 (Hepatic fibrosis), K74.1 (Hepatic sclerosis), K74.2 (Hepatic fibrosis with hepatic sclerosis), K74.3 (Primary biliary cirrhosis), K74.4 (Secondary biliary cirrhosis), K74.5 (Biliary cirrhosis, unspecified), and K74.6 (Other and unspecified cirrhosis of liver) (ICD-10 Version: 2019). The timeline covered by these data spans from January 1, 2015, to December 12, 2023.

National population statistics were sourced from the Bureau of National Statistics under the Agency for Strategic Planning and Reforms of Kazakhstan [15]. This dataset included the country's population numbers from January 1, 2012, to December 12, 2023, broken down by year. This information facilitated the calculation of LTx rates, the number of transplant centers per million population (pmp), and the prevalence of selected types of liver disease per 100,000 population.

2.2. Data analysis

All extracted data were organized in Excel spreadsheets. The Statistical Package for Social Sciences (SPSS) version 24.0 for Windows was employed for all data analyses in this study, with the significance level of all statistical tests pre-set at 0.05. The "Survival" function in SPSS was utilized to conduct the survival analysis of patients awaiting LTx in Kazakhstan. The primary variables were the date of registration on the waiting list and the date of death or the conclusion of the follow-up period (December 12, 2023). Life tables were computed to estimate cumulative survival at specific time intervals: 0 days, 30 days, 60 days, 90 days, 180 days, 360 days, 720 days, 1080 days, 1380 days, 1740 days, 2100 days, 2460 days, 2820 days, 3180 days, and 3540 days. The number of patients entering the interval and the number of patients withdrawing during the interval were documented. Cumulative mortality rates were calculated using the formula: 100 – cumulative survival. Kaplan-Meier analysis was employed to assess the probability that patients registered on the waiting list would survive until the end of the follow-up, as well as the mean and median survival with 95% Confidence Interval (CI). A graph reflecting the overall survival curve during the waiting period for LTx was generated.

The data of patients alive on the waiting list were analyzed in comparison with the data of patients who died without receiving LTx. Before analysis, the normality of data distribution was evaluated for continuous variables by computation of the Kolmogorov-Smirnov test and graphically, by generating histograms and Q-Q plots. Since the data distribution differed from normal, continuous variables were presented as median (Me) with 25th and 75th percentiles. Mann-Whitney U tests were employed for between-group comparisons. All categorical variables were presented as absolute numbers and percentages, and Pearson's chi-squared test was utilized for between-group comparisons.

The "Expert Modeler" function of SPSS was used to perform the time series analysis. As an initial step, annual nationwide prevalence rates of selected types of viral hepatitis (ICD-10 codes: B15.0, B16.0, B18.0, B18.1, B18.2, B18.8, and B18.9) and liver fibrosis and cirrhosis (ICD-10 codes: K74.0-74.6) were computed per 100,000 population for the period of 2015-2023. Additionally, the national pmp rates of LTx and

liver transplant centers were computed for the period of 2012-2023. The aggregated data encompassing annual prevalences, and the pmp rates of LTx and liver transplant centers, were organized in an Excel spreadsheet, indicating the reference year for the statistics. In the subsequent step, the best-fit epidemiological models for each type of predictive analysis were identified. The projections of the prevalence rates and pmp rates of LTx and liver transplant centers were made until 2030. The projections for 2025 and 2030 were reported as estimates along with their 95% CI, and corresponding graphs were generated.

2.3. Ethics approval

This study was conducted in strict accordance with the principles outlined in the Helsinki Declaration. Prior to the commencement of data collection, approval from the local ethics committee was obtained[16].

3. Results

In the period spanning 2012 to 2023, a total of 474 LTx surgeries were conducted in Kazakhstan. Among these, 411 procedures involved living donors, while 63 were sourced from deceased donors. Not a single DOMINO transplantation was performed during the study period. The pmp rates of LTx were notably higher for living donors in comparison to cadaveric transplantations. This disparity was most evident during the period of 2015-2017, with pmp rates for liver donor transplants recorded at 2.55, 3.18, and 2.86, respectively. Conversely, this same timeframe witnessed an increase in cadaveric liver transplantation rates, reaching 0.68 in 2015, 0.56 in 2016, and 0.61 in 2017. The initial rise in pmp rates for liver transplants for both living and cadaveric donors saw a decline in 2018. Subsequently, there was a resurgence in living donor transplants in 2021, although it did not reach the rates observed during 2015-2017 (Figure 1).

From 2012 to 2023, a total of eight liver transplant centers operated in Kazakhstan, serving a population of approximately 20 million people, as outlined in the Table 1. In 2012, when the first liver transplantation was performed in Kazakhstan, there was one liver transplant center conducting six surgeries. By 2013, the number of liver transplant centers had increased to five, with an average of 4.2 surgeries per center (ranging from 1 to 10). The peak number of liver transplant centers, seven in total, was reached in 2014 and 2015. During these years, the mean number of LTx per center was 4.57 in 2014 and 8.14 in 2015, with a maximum number of surgeries performed in one center reaching 8 and 13, respectively. The number of centers started to decline in 2016 and continued until 2020 when there were only two liver transplant centers nationwide. However, during this same period, the maximum number of LTx performed in one center reached its peak in 2017 (32 surgeries). Over the past three years (2021-2023), four liver transplant centers have been operational in Kazakhstan, with the mean number of surgeries per center exceeding 10.

A total of 364 patients were awaiting liver transplantation since the inception of the national waiting list in 2012, and unfortunately did not receive liver transplantation. Among them, 181 were deceased by the end of the follow-up period (December 12, 2023), while 183 remained alive. Table 2 presents comparisons between these two groups (deceased vs. alive) regarding age, sex, blood group, and RhD antigen, revealing no significant differences.

Table 3 provides insights into the survival of patients registered on the liver transplant waiting list. Out of the 364 patients, 6 had passed away on the day of registration on the waiting list, resulting in a cumulative survival rate of 92.0%. At the end of the first month after registration on the waiting list, 328 patients were still alive, yielding a cumulative survival rate of 87.0%. Three months after registration on the waiting list, 292 patients remained alive, and the cumulative survival rate was 83%. By the end of the first year of registration on the waiting list, only 209 patients were alive, resulting in a cumulative survival rate of 68.0%, which declined to 58.0% at the end of the second year and 52.0% at the end of the third year. The 10-year cumulative survival after registration on the waiting list was 27.0%, with only 7 patients alive.

Figure 2 illustrates the Kaplan-Meier survival curve of patients awaiting liver transplantation over a period of 4211 days, by the end of which the cumulative survival rate reached 0.0%. The mean survival time on the waiting list was 1834.702 days (95% CI, 1615.654; 2053.749), and the median survival time was 1273.0 days (95% CI, 876.611; 1669.389).

To illustrate the potential need for liver transplantation, an epidemiological analysis was conducted, including prevalence rates of selected types of liver disease that might necessitate liver transplantation. Over the period of 2015-2023, the highest prevalence rates were observed for chronic viral hepatitis B without the delta agent (ICD-10 code 18.1), increasing from 18.50 per 100,000 population in 2015 to 137.85 in 2023 (average annual increase of 28.13% (95% CI, 23.35; 33.10)). This was followed by chronic viral hepatitis C (ICD-10 code B18.2), which increased from 14.82 per 100,000 population in 2015 to 170.11 in 2023 (average annual increase of 35.29% (95% CI, 32.55; 38.08)). There was also an increase in the prevalence rates of liver fibrosis and sclerosis (ICD-10 codes: K74.0-74.6). The most substantial increase was observed in the rates of hepatic fibrosis with hepatic sclerosis (K74.2), rising from 0.51 per 100,000 population in 2015 to 7.72 in 2023 (average annual increase of 38.90% (95% CI, 33.06; 44.99)) (Table 4). Table 5 presents estimates of projected prevalence rates of selected types of viral hepatitis and liver fibrosis and cirrhosis. The forecasts of liver disease are accompanied by projections of pmp rates of LTx and liver transplant centers in 2025 and 2030. According to projections, the rate of viral hepatitis with the potential to require liver transplantation will increase to 501.94 per 100,000 population in 2025 and 1081.37 in 2030, while the rate of liver fibrosis and cirrhosis will experience a more abrupt increase (54.87 per 100,000 population in 2025 and 121.04 in 2030). However, the projected pmp rates of liver transplant centers and liver transplant surgeries will remain the same in both 2025 and 2030. Figure 3 supplements the findings of Table 5, providing a graphical representation of projections until 2030. Although the forecast curves show an increase in prevalence rates for both viral hepatitis and liver fibrosis and cirrhosis, the

curves remain stable for rates of liver transplant centers and transplant surgeries.

4. Discussion

To the best of our knowledge, this study is the first attempt to evaluate the performance of Kazakhstan's national LTx service from its inception in 2012 to the current date in 2023. The overall pmp rate of LTx ranged from 0.35 (2012) to 3.77 (2016), and LTx from living donors surpassed those from deceased donors multiple times. Throughout the analyzed period, the count of liver transplant centers fluctuated between 1 and 7 for a population of approximately 20 million people, resulting in pmp rates ranging from 0.06 to 0.40. A total of 474 patients underwent LTx, while another 364 patients were on the waiting list but did not receive transplantation. Among these, 181 patients were deceased, and 183 were still alive by the end of 2023, with no significant differences observed between these two groups. The 30-day cumulative survival on the waiting list was 87.0%, and 1-year survival was 68.0%. The prevalence of selected types of viral hepatitis and liver cirrhosis steadily increased from 2015 to 2023, and projections suggest this trend will persist until 2030. Without targeted interventions, the pmp rates of LTx and liver transplant centers are expected to remain stable, contributing to the backlog of unoperated patients awaiting transplantation. These findings warrant a more in-depth discussion.

According to the GODT data, in 2022, Kazakhstan ranked 11th in the list of countries based on pmp rates of LTx from living donors, dropping from its 8th position in 2021. However, the overall pmp rates of LTx in Kazakhstan are relatively low, with the country ranking 48th out of 91 countries in 2021 and 51st in 2022. Nonetheless, Kazakhstan stands out as the leader in LTx activities in Central Asia, surpassing other countries in the region in pmp rates. When compared with other post-Soviet countries, Kazakhstan ranked 5th in 2022 and 2021, following Lithuania, Belarus, Estonia, and Georgia. In general, the pattern of LTx activities in Kazakhstan mirrors that seen in the South-East region, characterized by a significant predominance of LTx from living donors and relatively lower overall pmp rates [10].

Regarding transplant centers, the pmp rates observed in Kazakhstan were lower than those in other global regions. For instance, in 2022, the region of the Americas had 2.4 liver transplant centers pmp, Europe had 3.0, the South-East region had 6.7, the Western Pacific region had 7.7, and the Eastern Mediterranean region exhibited the highest pmp rates of liver transplant centers at 13.2 [10]. The number of liver transplant centers in Kazakhstan is comparable to that in the United Kingdom, where there are seven centers for a population of approximately 64 million people [17]. When considering the number of LTx surgeries performed in Kazakhstan, the liver transplant centers appear to be low-volume, with the majority conducting fewer than 10 LTx per year. The only high-volume center in the country, the National Scientific Center of Surgery named after Syzganov, performed a maximum of 32 LTx per year.

Presently, LTx services in the country are provided free of charge to residents, funded by the health insurance fund. This funding encompasses the surgical costs for both the recipient and the donor. However, ancillary expenses such as pre-surgical examinations, tests, and post-surgical rehabilitation often incur out-of-pocket expenses [18]. There are no imposed budget constraints on the quantity of LTx procedures conducted in the country. Nevertheless, the relatively low rates of LTx are attributed to the opt-in approach adopted in Kazakhstan [19]. Under this approach, consent for organ donation after death must be obtained, typically granted by the deceased's relatives in the absence of a declared will [20]. Generally, the opt-in approach tends to yield fewer organ transplantations compared to the opt-out approach, where all deceased individuals are automatically considered potential donors. Experiences from the European region demonstrate that countries adopting the opt-out approach tend to have higher LTx rates [21]. It's worth noting that Kazakhstan used to have an opt-out system, leading to more organ transplants between 2015 and 2017. However, this changed after an incident in 2017-2018 when some transplant surgeons were accused of mishandling organ transplants. Even though they were eventually cleared of all charges [22], this incident had a lasting impact, and pmp rates haven't reached the levels of 2015-2017 even after six years.

The Transplantation Coordination Center functions as a non-profit organization, serving as the national intermediary among 40 donor hospitals and 4 transplant centers. This center consolidates information on patients eligible for LTx into a unified national waiting list. The criteria for notification from donor hospitals to the Transplantation Coordination Center involve potential donors meeting the criterion of brain death; currently, donation after circulatory death is not practiced. Throughout the study period, there was no cross-border exchange of donors or recipients with other countries in the region, and all liver transplants were exclusively performed on Kazakhstani citizens. The indication for liver transplantation is determined by a Child-Turcotte-Pugh score of 7 or higher (classes B and C) [6], with the Model for End-Stage Liver Disease (MELD) not currently in use. The survival analysis reveals a notable proportion of patients facing mortality shortly after entering the waiting list, indicating a 13% cumulative one-month mortality. This underscores the potential benefits of earlier inclusion in the waiting list for these patients.

Globally, over the past decade, there has been a shift in the indications for LTx. End-stage liver cirrhosis remains a major indication [23], aligning with the national standards of LTx in Kazakhstan (Clinical protocol, 2019). However, the global etiology of liver cirrhosis has changed, moving away from viral hepatitis due to the availability of effective antiviral medications and shifts in lifestyle and dietary approaches. In Kazakhstan, the burden of viral hepatitis is substantial and continues to grow, as indicated by our findings and earlier scientific data [24]. Direct-acting antiviral hepatitis C drugs have not gained widespread use in Kazakhstan, and despite anti-viral hepatitis B vaccination being included in the national vaccination schedule in 1998, the prevalence of anti-HBcore antibodies was reported to be 17.2%, surpassing rates in many other countries [25]. The projections of viral hepatitis and liver cirrhosis until 2030 indicate a likely increase in these diseases' prevalence, suggesting

a rising demand for LTx. Public health action is imperative to augment LTx activities in Kazakhstan to meet the growing demand for LTx surgeries.

5. Limitation

This study has several limitations. The primary limitation is that the data available in the national waiting list of patients awaiting LTx are limited, with many specific details related to underlying diagnoses missing. This limitation makes the calculation of cause-specific survival impossible and restricts the analysis of associated risk factors. Another limitation arises from the fact that forecast modeling utilized prevalence rates of selected types of viral hepatitis and liver fibrosis and cirrhosis, but data on end-stage liver disease were not available, as the study solely relied on ICD-10 codes, thereby limiting the capacity of projections. Additionally, the projected rates of both liver disease prevalence and LTx rates should be interpreted with caution, as they serve as an illustration of the need for public health action to address the existing situation. Nonetheless, this study boasts several strengths, the most notable being its status as the first nationwide study analyzing the outputs and outcomes of LTx services.

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