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Evolution of Indications for Liver Transplantation (LTx) in the Years 2001–2017 in Poland

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Hepatitis B and C viruses have been recognized as undoubtedly carcinogenic to humans. In the Polish population, where most people are protected by HBV vaccinations, hepatocellular carcinoma (HCC) and its main cause, persistent HCV infection, significantly affect the demand for liver transplantations.

Material/Methods: The purpose of this study was to categorize the number of primary liver transplantations in Poland in the years 2001–2017 by cause and to analyze changes in LTx indications during this period. Data were sourced from POLTRANSPLANT, the Organization and Coordination Center for Transplantation in Poland. Additionally, we compared the numbers of HCC cases and hepatitis B and C cases during this period.


Results: In the analyzed period, in Poland, 3332 primary liver transplantations were performed. Overall, 44% (1456) of LTx cases were combined with HBV and/or HCV and/or HCC. In this group, transplants in patients with only 1 specific factor – HCV – formed the largest cohort, accounting for about 40% (581) of cases. Transplants in patients who only had HBV and in those who only had HCC accounted for 12% (185) and 5% (69), respectively.

Conclusions: The analyzed data suggest that HCV infections are a significant public health problem in Poland, as is also reflected by the growing number of LTx performed due to HCC. To limit the numbers of HCV and HCC cases, immediate implementation of a Polish National Program against HCV should be considered.

MeSH Keywords: **Carcinoma, Hepatocellular • Hepatitis B • Hepatitis C • Liver Transplantation • Poland • Public Health**

Abbreviations: **HBV** – hepatitis B virus; **HCV** – hepatitis C virus; **HCC** – hepatocellular carcinoma; **LTx** – primary liver transplantation; **ECDC** – European Center for Disease Prevention and Control; **WHO** – World Health Organization; **IARC** – International Agency for Research on Cancer

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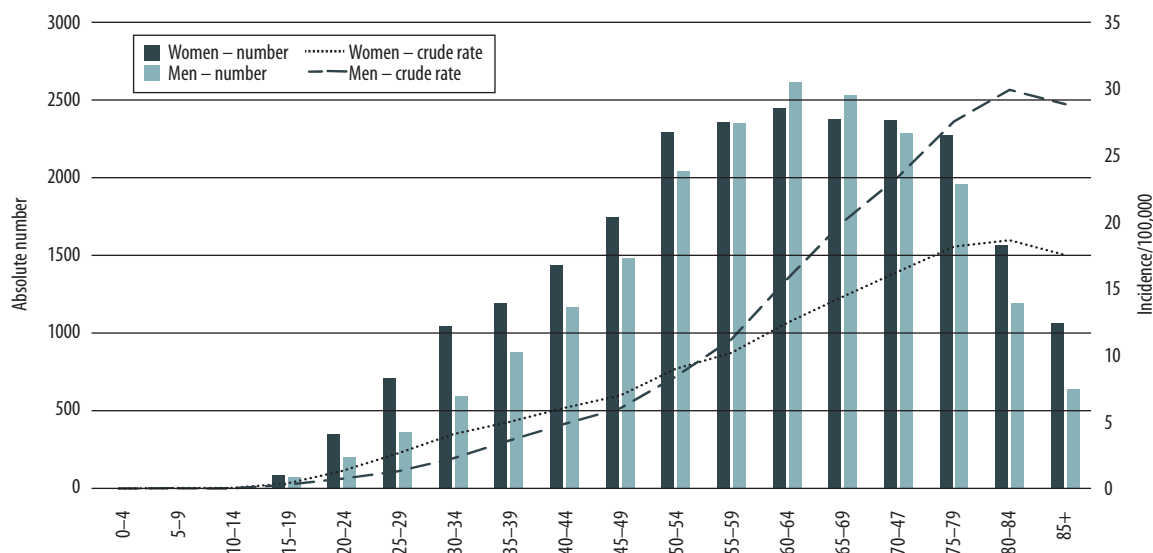
1 Background

During the last 5 decades, transplants have become the standard and often the only method of treatment for many patients. In the case of liver transplantations, the main causes are chronic HBV and/or HCV infections and their cause, HCC. These viruses have been classified by the International Agency for Research on Cancer (IARC) as undoubtedly carcinogenic to humans (group 1) [1].

The World Health Organization (WHO) estimates that about 500 million people worldwide are infected with HBV or HCV. Moreover, in the WHO European Region, about 13.3 million people currently live with chronic hepatitis B (about 1.8% of all adults) and 15 million have chronic hepatitis C infection (about 2% of the adult population). According to data from the European Center for Disease Prevention and Control (ECDC), in the European Union countries, the overall hepatitis B incidence is 1.49/100,000 and 8.7/100,000 for hepatitis C. The very high incidence of infections among people who inject drugs is especially concerning [2]. Geographically, the great majority of HBV infections are in the WHO African and Western Pacific Region, whereas for HCV infections the regions with the highest prevalence are the WHO European Region and the WHO Eastern Mediterranean Region [3].

In Poland, there are approximately 130,000 people currently infected with the HCV virus and 300,000 with HBV infection [4,5].

According to the National Cancer Registry data, the number of HCC cases in the years 2001–2016 was growing. Most importantly, among all liver cancer types, HCC is the most characteristic for people about 50 years old, as risk of the disease grows with age (Figure 1).



53 Figure 1. All liver cancer cases (absolute number and crude rate) by sex and age groups in the years 2001–2016 in Poland [6].

Material and Methods

The purpose of the study was to categorize the numbers of primary liver transplantations in Poland in the years 2001–2017 by cause and to analyze changes in LTx indications in this period. Data were sourced from POLTRANSPLANT, the Organization and Coordination Center for Transplantation in Poland. The total number of LTx analyzed was 3332. We compared numbers of HCC cases (N=8023) (without data from 2017) between those with hepatitis B (N=35 282) vs. those with hepatitis C (N=46 957) in the relevant period. Data on HCC cases were sourced from the National Cancer Registry in Poland, while data on hepatitis C and B were collected from the annual publication “Infectious diseases and poisonings in Poland” prepared by the National Institute of Public Health, National Institute of Hygiene and Chief Sanitary Inspectorate in Poland (2001–2017). The resulting database was analyzed in Microsoft Excel.

Limitations of the study

Some of the obtained data are estimates. Some of the changes found could have resulted from improved reporting. Data on the occurrence of hepatitis B and C may have been underestimated due to the large number of undiagnosed cases.

Results

The analysis of the received data suggests that HBV and HCV infections, as well as HCC, are among the most frequent indications for primary liver transplantations in Poland in the years 2001–2017. In the analyzed period, overall, about 44% (1456)

1 Table 1. Number of primary liver transplantations (LTx) by year and cause in the years 2001–2017 in Poland [7].

Year	Only HCV	HCV with HCC and other diseases but not HBV	HCV with other diseases but not with HBV and HCC	Only HBV	HBV with HCC and other diseases but not HCV	HBV with other diseases but not with HCV and HCC	Only HCV with HBV	HCV, HBV and HCC, with other diseases	HCV, HBV with other diseases but not with HCC	Only HCC	HCC with other diseases but not with HCV and HBV	Other indications excluding HCV, HBV and HCC	In total
2001	10	–	–	6	–	–	–	–	–	1	–	78	95
2002	22	–	1	11	–	–	1	–	–	5	–	87	127
2003	28	1	–	6	1	3	1	–	1	5	–	102	148
2004	32	1	4	11	–	2	8	–	–	1	–	108	167
2005	41	4	1	9	2	2	7	1	1	1	–	118	187
2006	33	2	7	12	–	–	6	–	–	2	–	106	168
2007	31	6	9	11	1	3	7	–	–	1	–	103	172
2008	41	6	4	13	3	–	4	2	–	2	–	135	210
2009	41	11	3	17	8	1	1	2	–	3	1	108	196
2010	30	8	1	10	1	1	5	–	–	10	1	136	203
2011	37	12	4	19	2	2	5	1	–	12	1	173	268
2012	46	25	6	21	6	7	15	4	–	7	12	143	292
2013	39	38	4	12	5	6	21	7	–	2	7	155	296
2014	30	48	6	6	6	10	13	14	1	5	8	167	314
2015	41	32	2	8	10	8	7	6	1	3	11	157	286
2016	41	40	–	5	3	–	4	3	5	3	1	–	105
2017	38	32	–	8	6	1	–	2	5	6	–	–	98
In total	581	266	52	185	54	46	105	42	14	69	42	1,876	3,332

35 of LTx cases were combined with HBV and/or HCV and/or HCC. In this group, transplants performed in patients who only had 1 specific factor – HCV – were also a large cohort (about 40%) (581). Transplants performed in patients who only had HBV and in those who only had HCC accounted for 12% (185) and 5% (69), respectively. In the analyzed group, another relatively large cohort (18%) was transplant cases who had both HCV and HCC (266). Within the analyzed period, this group also showed the most significant increase in the number of cases – from 0 in 2001 and 2002 to 32 in 2017 (and 48 cases in 2014).

45 The lowest number of primary liver transplantations was performed among patients who had HBV and HCV infections and other diseases at the same time (but not HCC) – about 1% (14). Other rare indications for primary liver transplantation were HCV, HBV and HCC with other diseases (about 3%) (42), and HCC with other diseases but not with HCV and HBV (about 3%) (42) (Table 1).

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As the strongest factors leading to the need for LTx were HCC, HBV, and HCV, we also decided to analyze epidemiological data on incidence of these factors for a similar period in Poland. In accordance to the analyzed data on HCC and hepatitis B and C in Poland in the years 2001–2017 (without data from 2017 for HCC), an increasing incidence trend was observed. The number of cases of all liver cancer types in Poland in the years 2001–2016 was similar and represents a stable trend, but after isolation of the HCC cases, an increasing trend of the number of these cancers is visible (Figure 2).

45 Over this period, the percentage of HCC cases among all liver cancer types increased significantly. In 2001, only 17% (274) of all liver cancer cases were diagnosed as having HCC, but at the end of the analyzed period in 2015 and 2016 it was 50% (766) and 48% (705), respectively (Table 2), which is also reflected in LTx demand.

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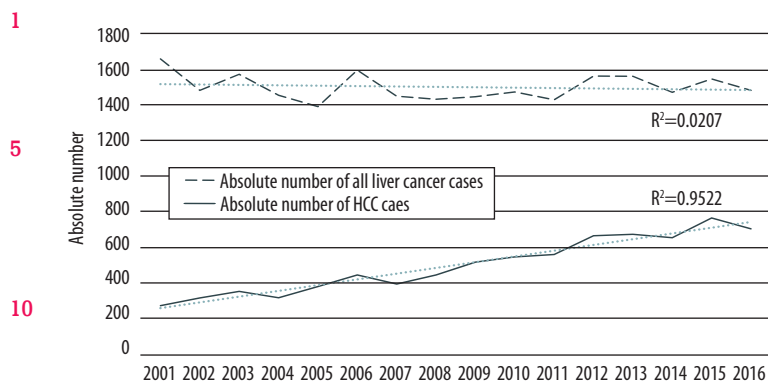


Figure 2. Changes in the number of liver cancer cases for all types and HCC cases in the years 2001–2016 in Poland [8].

Table 2. HCC cancer cases – HCC percentage (of all liver cancer cases) and absolute numbers in the years 2001–2016 in Poland [8].

Year	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Percentage (%)	17	21	23	22	27	28	27	31	36	37	39	43	43	45	50	48
Number	274	317	354	318	381	446	395	446	518	547	561	666	674	655	766	705

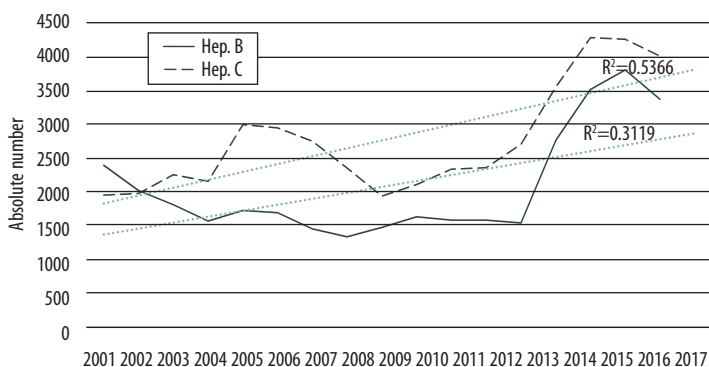


Figure 3. Changes in the number of hepatitis B and hepatitis C cases in the years 2001–2017 in Poland [9].

Similar to the data on HCC, epidemiological data on hepatitis B and C indicates the growth of the number of cases in the years 2001–2017 (Figure 3). A significant increase in hepatitis B and C cases was observed in 2014. In comparison with 2013, in 2014 there were 1222 more hepatitis B cases, which means that the incidence per 100,000 population had increased from 4 to 7.18 and became even higher in the following years. Likewise, in the case of hepatitis C, there was growth of about 845 cases and the incidence per 100,000 increased from 7.03 in 2013 to 9.23 in 2014, and was even higher in the following years. The small decrease in the number of cases in 2017 is a probable artefact that will be corrected when data is updated, as it was in previous years (Figure 3, Table 3).

The obtained data also proved that hepatitis C was much more common than hepatitis B and HCC in the Polish population for most of the analyzed period, which also is associated with LTx demand. This was observed since 2003, when a trend reversal

took place. In the years 2001 and 2002, the number of hepatitis B cases was higher than hepatitis C cases, by about 441 and 43 cases, respectively (Figure 3, Table 3).

Discussion

The obtained data suggest that one of the most frequent indications for primary liver transplantations in Poland in the years 2001–2017 was the combination of HBV, HCV, and HCC infections in various combinations (joint and separate occurrence) (Table 1). A similar conclusion was reached by Crespo et al., who found that hepatitis B and C viruses, as well as HCC, were the most typical indications for liver transplantations [10]. Moreover, Farkas et al. argue that for patients with complications such as HCC, liver transplantation is the only treatment option [11].

Table 3. Absolute numbers and incidence of hepatitis B and C cases in Poland in the years 2001–2017 [9].

Year	Hepatitis B		Hepatitis C	
	Incidence/100,000	Absolute number	Incidence/100,000	Absolute number
2001	6.2	2,394	5.05	1,953
2002	5.29	2,021	5.17	1,978
2003	4.74	1,812	5.9	2,255
2004	4.11	1,570	5.65	2,157
2005	4.53	1,727	7.85	2,997
2006	4.44	1,693	7.73	2,949
2007	3.81	1,454	7.22	2,753
2008	3.51	1,337	6.17	2,353
2009	3.87	1,475	5.08	1,939
2010	4.28	1,633	5.53	2,111
2011	4.11	1,583	6.07	2,338
2012	4.11	1,583	6.12	2,359
2013	4	1,541	7.03	2,706
2014	7.18	2,763	9.23	3,551
2015	9.15	3,518	11.14	4,285
2016	9.9	3,806	11.09	4,261
2017	8.78	3,372	10.44	4,012

In the analyzed group, the highest number of LTx was performed among patients who demonstrated persistent HCV infections with or without HCC. Graziadei et al. also state that in many European and American countries, chronic HCV infection is the leading or second indication for liver transplantation [12]. The obtained results also suggest the smaller role played by HBV on LTx demand. The reason behind this phenomenon can be found in the introduction of the vaccine against hepatitis B into the vaccination program in 1989. At the beginning of the 1990s, a decrease in hepatitis B occurrence was observed due to the introduction of the program for the prevention and eradication of hepatitis B. Additionally, across the country, screening of blood and organ donors and enhanced protection in hospitals were introduced. Kowalska et al., however, found that in recent years in Poland there is has been a clear plateau trend in hepatitis B cases, and the disease is now more often detected, especially among young adults (older than 35 years) who have not been vaccinated as part of the vaccination program [13]. In 2015, Poland introduced direct-acting antiviral treatment (DAA), which is characterised by very high effectiveness, better tolerance than interferon treatment, and shorter time of admission (12 weeks) [14]. Non-interferon treatment is reimbursed by the National Health Fund as part of the therapeutic drug program led by the Ministry of Health in Poland [15]. However, the obtained data do not reflect this important achievement. A possible

explanation is the short time since the program's introduction, as well as the high percentage of people who are not aware of their infection. The most recent reports estimate that there are about 150,000 people (about 0.5–1% of the population) in Poland with chronic HCV infection, 80% of whom are not aware of this fact [4,16,17].

The obtained data on HCC show that this type of liver cancer in the analyzed period was becoming more frequent, and its effect on liver transplantation demand could become more visible in the future. Flisiak et al. presented 3 scenarios on the development of HCV incidence in Poland until 2030. One of the scenarios assumes a significant increase (60%) in HCC incidence related to HCV (1250 cases) until 2030 [18]. Taking into consideration the presence of other strong risk factors that play key roles in cancer development in general and specifically in HCC, we can assume that primary liver transplantations caused by HCC will become more frequent due to factors such as the aging of Polish society and increased alcohol intake. The vast majority of liver cancer cases occur among people aged 55 years and older (about 82% among men and 88% among women). The risk of this disease increases with age and is the highest in the ninth decade of life for both sexes [19]. Moreover, the State Agency for the Prevention of Alcohol-Related Problems in Poland reported an increasing trend in alcohol consumption. In 2017, each citizen on average drank 3.3

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1 litres of alcohol. In comparison, in 2007 and 1997 this was 3.0 and 2.8 litres per person, respectively [20].

To date, there is no national program targeting the eradication and prevention of HCV infections in Poland. Moreover, coordinated HCV screening is still unavailable at the level of primary healthcare. In 2013, National Health Fund expenditures for HCC treatment and liver transplantations was 16.8 and 17.8 million PLN, respectively. These were only direct costs incurred by the taxpayer and are probably significantly underestimated [21].

Hepatitis B and C are the main causes of HCC worldwide and are responsible for about 77% of cases of this type of cancer [22]. These 3 main reasons for primary liver transplantations are caused by these 2 viruses, which are completely modifiable risk factors. The introduction of effective primary prevention solutions, as well as improvement of the currently existing ones, would be beneficial both for patient health and for the budget of the National Health Fund. An example of spectacular results delivered by reducing exposure to modifiable risk factors is the decline in the incidence and mortality rates of stomach cancer in Poland. Among others measures, the introduction of effective antibiotic therapy prompted an almost 3-fold decrease in stomach cancer cases during the last 4 decades [23]. Another good example showing the effect of the elimination of infectious factors leading to severe health consequences comes from Australia. Since 2007, Australia has run a vaccination program for HPV eradication (for girls and boys),

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which is expected ultimately to eliminate HPV in the next 2–3 decades in that country [24].

Conclusions

1. In the analyzed period in Poland, dominant indications to LTx were cases with HCV infections and HCC.
2. It is hard to estimate future changes in LTx indications due to the coexistence of contradictory factors influencing LTx numbers in Poland (for example, the available anti-HCV treatment and the many people who are not aware of their infection). Conversely, the results of the study may suggest that the number of primary liver transplantations due to HCC could increase in the future based on further increases in HCV incidence and/or alcohol consumption and/or population aging.
3. The analyzed data suggest that HBV and HCV infections are a significant public health concern in Poland. In order to limit HCV and HCC cases, the immediate implementation of a Polish National Program against HCV should be considered. There is also a need to pay more attention to the prevention of HBV infections by educating and vaccinating people who do not currently have access to the vaccination program.

Conflict of interest

None.

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