Peri-operative Anesthetic Management in Liver Transplantation

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Nikunj Gupta
Annu Sarin Jolly
Seema Bhalotra
Editors

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Preface

Liver transplantation is relatively a new specialty with first successful transplant being performed in the year 1967 by Thomas Starzl, and in India it was performed in 1998. The journey of transplantation in India has been very lucidly described in the chapter on history of liver transplantation in this book by Prof Samiran Nundy. Over the last 15–20 years, liver transplantation has gained momentum in the Asian subcontinent. If there were ten established centers in India doing liver transplantation in the year 2000, now there are over 135 centers doing liver transplantation and more centers are coming up. There are many textbooks available on the subject, but very few resources are available dealing with the perioperative care of patients with end-stage liver disease needing liver transplant. The surgical aspects are widely covered in these books with scant reference to the anesthetic and perioperative care of these patients. It was felt that there was a need to have a book which provided information on this aspect of patient care in patients with end-stage liver disease. There is another motivational reason to take on this assignment to get this book published. Our group under the leadership of Dr AS Soin were among the firsts to start liver transplants in India, initially at Sir Ganga Ram Hospital and then at Medanta Hospital, Gurgaon. On starting the training program of Fellowship in Liver Transplant Anaesthesia at Medanta from the year 2012, we felt at a loss to provide the fellows enough reading material or a textbook on the subject. Although in this era of Internet there is information available at the touch of a button, it is all scattered. Our fellows were provided with a collection of good articles to make a beginning. There was always something missing—a book to refer to, which had most of the basic information for perioperative care of liver transplant patients. Therefore our team of editors got together and decided to embark on this journey of getting this book together. The authors were identified who had good experience in this growing specialty. Of course everything was not straightforward and many authors had to be substituted for various reasons.

So the aim was to have a collection—book, which covers the perioperative care of liver transplant patients which would be useful for trainees as well as for practicing anesthesiologists, intensivists, and those responsible for the perioperative care of transplant patients. There is slightly more attention given towards living donation liver transplantation in the book as this is the dominant part of liver transplant program in India as of now.

In India, most of the transplantation activity is confined to living donor liver transplantation, whereas the deceased donor transplant is still not practiced very frequently due to lack of availability of organs. Looking at the figures for the year 2020, there were around 16.3% deceased donors (GODT—Global Observatory on Donation and Transplantation), the rest being living donor transplant. This is one area that needs to be looked at critically—improving deceased organ donation. I must express my sincere gratitude to Prof Samiran Nundy who has been motivating us in this venture and has been in constant touch regarding the progress of the book. He is the one who was also instrumental in bringing the Human Organ Transplant Act (1994) in India, initiating and giving impetus to the liver transplant activity.

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About the Editors

Vijay Vohra is Chairman, liver transplant, GI anesthesia, and intensive care at Medanta The Medicity, Gurgaon, India. He has 37 years' experience in anesthesiology after qualification. He headed the team that established liver transplant anesthesia and critical care at two major centers in India (SGRH and Medanta). He has 5 years' experience as Vice-Chairperson in policy making and running a large department of 40 anesthetists. Dr Vohra has imparted training in transplant anesthesia to visiting/fellow anesthetists and intensivists from 26 centers within India and abroad in the last 10 years. He has an experience of nearly 3000 liver transplants—among the highest anywhere. Dr Vohra is first in India to develop and introduce hemodynamic and coagulation monitoring protocol for bloodless liver transplant. He headed the anesthesia team that participated in almost all the firsts in liver transplantation in India. He has been a DNB teacher for 17 years. Dr Vohra has special expertise in anesthesia in liver transplant, kidney transplant, GI surgery, and vascular surgery. He is regularly invited as faculty to national and international conferences.

Nikunj Gupta is a Diplomate in National Board (DNB) qualified anesthesiologist and has an experience of over 20 years in the specialty. He has been involved in the care of liver transplant patients for nearly 18 years. For the last 12 years, he been practicing perioperative care of liver transplant patients at Medanta The Medicity, Gurgaon, India. He has been involved in the training of fellows admitted for liver transplant anesthesia at Medanta The Medicity.

Annu Sarin Jolly has over 20 years of experience as a consultant anesthesiologist in leading multispecialty hospitals of Delhi, India. Her area of interest is liver transplantation. She trained at the best centers of Delhi like Apollo, Sir Ganga Ram Hospital, and Medanta and had the privilege of working with pioneers in the field like Dr Soin and Dr Vijay Vohra, who have been her mentors. Currently, she is the clinical lead anesthesia at Narayana Health and conducts liver transplant anesthesia across its pan-India branches. She is also involved with pediatric transplants in NH SRCC Children's Hospital, Mumbai.Dr Annu has authored several national and international papers and contributed to a textbook on laparoscopic anesthesia before this. She has been actively involved in organizing seminars and teaching liver transplant fellows. She is also a DNB teacher and has several presentations to her credit.

Seema Bhalotra is a senior consultant, anesthesia and critical care medicine. Have practiced anesthesia in leading multispecialty hospitals like Ganga Ram hospital, New Delhi, and Medanta, The Medicity, Gurugram. Have a keen interest in liver transplant and gastrointestinal surgeries. Practiced liver transplant anesthesia for 8 years in a leading liver transplant center of India. Have been associated with teaching and training of DNB anesthesia and fellowship in liver transplant students. Have multiple national and international poster presentations and have contributed to chapters in anesthesia-related books.

The History of Liver Transplantation in India

1

Samiran Nundy

1.1 Introduction

In 1988 starting a liver transplantation programme in India seemed to be a distant dream for many of us because there were so many hurdles to overcome—it was an exorbitantly costly procedure, there was no local expertise available at that time, the trade in human organs especially kidneys was widespread and the law only recognised cardiorespiratory death and not brain death so that transplants from beating heart donors could not be done. However with a consistent and combined effort we were able to overcome most of these problems gradually and, although some still remain, we have reached a stage where there are now 135 centres in this country which have been registered to carry out liver transplants and, till May 2019, 16,806 procedures had been performed with the results in some centres matching the world's best. And India does the fourth largest number of liver transplants internationally following the USA, China and Korea.

In this chapter I will chronicle our journey from how it all started to where it has reached and although it is, of necessity, a rather personal account, I wish to pay tribute to many of the generally unnamed doctors, journalists, bureaucrats and politicians who helped bring about this momentous change.

1.2 Background

In 1988 there were an estimated 120 centres elsewhere in the world performing 4500 liver transplants annually with an 80% success and 70% five-year survival rates. In stark contrast, there was no liver transplant facility in India and there were an estimated 300,000 deaths from liver failure annually. A small group of us made an initial attempt to sensitise the public to this problem through popular television programmes like 'The World this Week' as well as articles in newspapers and medical journals. But probably the main impetus was provided by the then Prime Minister, Shri Rajiv Gandhi who, after one of his trips abroad, asked the Health Minister why heart and liver transplants were not being done in this country. The Health Secretary then constituted a small group of four people to report on this and we defined the problems that had to be overcome, i.e. the cost, the lack of local expertise, the organ trade and the absence of a law which recognised brain death. To move forward we identified the first move should be to educate the public on the benefits of starting a liver transplant programme in India.

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1.3 Step I: Public Education

This was done through a series of newspaper articles and television appearances. Although there were major opponents to starting such a programme—it would cost 20 lakhs, there would be an enormous wastage of blood and blood products (the blood requirement for a single procedure was usually about 20 units at that time; now it is about 4–6 units); it would become the focus of hospital attention and distract from many other activities which benefited many more people. It was likened to having a 'CT scanner on a malarious swamp'!

The counterarguments were that the procedure would save many young productive lives, it would be available locally, the cost would be much lower than it was in western countries, the quality of doctors and hospitals would be upgraded and there would be national pride that such high-end medical care was available in our own country. No longer would our very rich compatriots need to go abroad for transplants where they were placed at the bottom of the waiting lists and often received 'marginal' livers that had been rejected for use in the indigenous population. We held conferences and workshops in Calcutta, Bombay, Madras and Delhi to which we invited prominent social workers, journalists and religious leaders to discuss whether the concepts of brain death and liver transplantation were acceptable and necessary. There was a generally positive response. The next step would be to try and change the existing law defining death and to allow beating heart organ transplantation.

1.4 Step 2: Changing the Law

After the conference in Delhi in 1991 the government appointed a small committee chaired by Dr. L.M. Singhvi, the eminent lawyer, to examine and report on the concept and definition of brain death, its desirability and implications, to suggest safeguards against misuse and how it might facilitate the availability of organs such as the heart and liver for transplantation.

The Singhvi Committee presented its report to the Cabinet and the Bill was placed in 1992 before the Rajya Sabha where it received overwhelming support. However when it went to the Lok Sabha there were serious objections raised to some of its clauses like including only first-degree relatives as living donors and it was referred to a Select Committee for further debate. Two years passed without any progress and we felt that the law would never be passed but in 1994 the Bill was placed before the Lok Sabha again and after a brief debate in a sparsely attended house it was accepted. The Transplantation of Human Organs Act became a law in 1995.

Its rules stated that only registered hospitals would be allowed to perform transplantation and listed the criteria for organ retrieval. Brain death would be determined by clinical tests alone, i.e. the cause of coma should be known, there would be an absence of cranial reflexes and there should be a positive apnoea test. All these would be verified twice by four specially designated doctors 6 h apart.

An 'Appropriate Authority' was also created which would be responsible for the registration of hospitals, maintenance of standards, would investigate breaches of the law and audit the indications and results of the transplant procedures. For living transplants only first-degree relatives would be allowed to donate organs but if the recipient did not have a suitable donor then someone 'emotionally' related would be permitted to donate. The 'emotional' attachment would by verified by a designated 'Authorisation Committee'.

Trading in human organs was made illegal and a non-cognisable offence.

1.5 Step 3: The Initial Procedures

The first procedure after the Bill was passed was a heart transplant done in the All India Institute of Medical Sciences (AIIMS), New Delhi, by Dr. P. Venugopal and was a success. It was announced by the then Prime Minister, Shri Atal Behari

Bajpayi, in Parliament to loud cheers. However liver transplantation took a long time to gain any sort of momentum. There were a few performed, mostly unsuccessfully, in 1995 in the Apollo Hospital, Chennai, and then at AIIMS Delhi. The first successful deceased donor liver transplant was done on a 43-year-old man in the Apollo Hospital, Delhi, on November 6, 1998, by Dr. AS Soin and Dr. MR Rajasekar. This patient lived for 12 years after the transplant. He had recidivism and died of recurrent alcoholic cirrhosis of his transplanted liver. The second successful transplant in India was a live donor (left lateral sector) liver transplant on November 15, 1998, on an 18-month-old male child with biliary atresia. This patient is alive and well.

1.6 Step 4: Sustainable Programmes

1.6.1 Numbers

In spite of the law being passed there were very few deceased donor transplants and the main activity, albeit small in number, was centred around living donors (Fig. 1.1).

There were very few done up to 2008 after which there was a spurt in activity after the year 2009 with a gradually increasing number of deceased donors especially in Tamil Nadu. The main impetus for this increase was the farseeing Tamil Nadu Government orders of 2008 which made brain death declaration mandatory and doctors who were in charge of such patients were required to ask their relatives for organ donation. It also decreed that a State level waiting list be maintained, laid down norms on how the procured deceased organs should be distributed, required that Transplant Coordinators should be appointed in all registered hospitals, provided government subsidies of up to 30 lakhs towards the cost of the procedure, established 'green corridors' so that the harvested donor organs could be moved quickly in spite of heavy traffic to the recipient hospital and supported non-governmental organisation such as the MOHAN Foundation which has done such sterling work in promoting deceased organ donation throughout the country.

In 2011 there were amendments to the existing law passed by Parliament which mandated a video recording of Authorisation Committee meetings, delinked transplantation registered institutions from those which could diagnose brain death, allowed intensivists and one other doctor to confirm the diagnosis (rather than the four designated doctors, including neurosurgeons, previously), included grandparents and uncles as near relatives and allowed 'swap' donations across family members according to blood group matching. It also established the NOTTO, ROTTO and SOTTO (National, Regional and State Organ and Tissue Transplant Organisations) in addition to the already existing ORBO (Organ Retrieval and Banking Organisation).

Thus Fig. 1.2 shows the rapid increase in liver transplant numbers since 2009 when there were

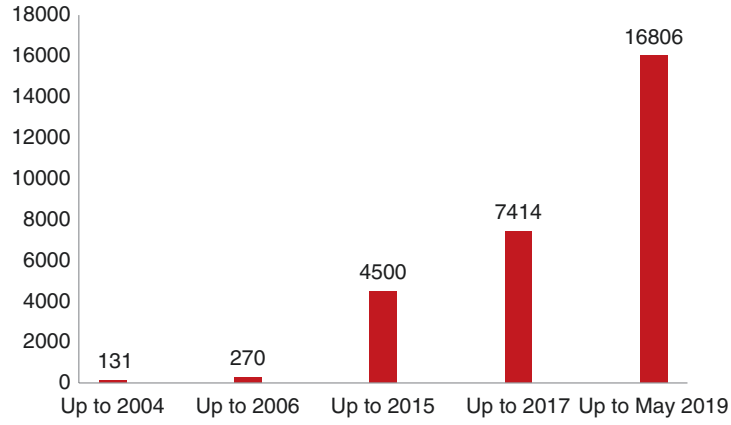

Fig. 1.1 Liver transplantation activity in India up to May 2019

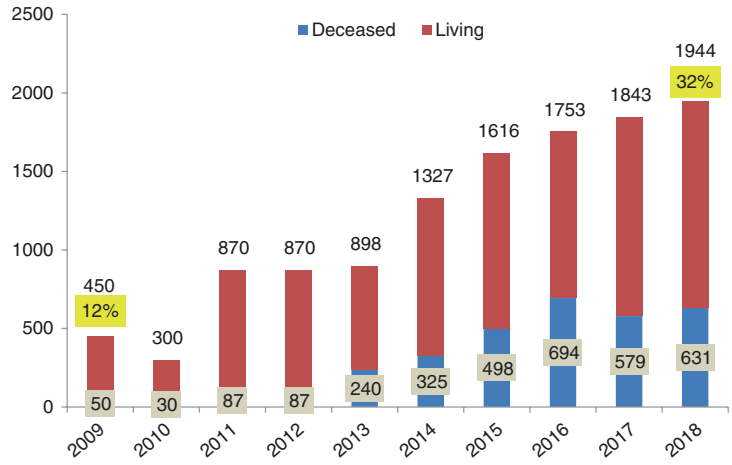

Fig. 1.2 The total transplants performed annually in India between 2009 and 2018 with the numbers and proportions of deceased and living donor procedures

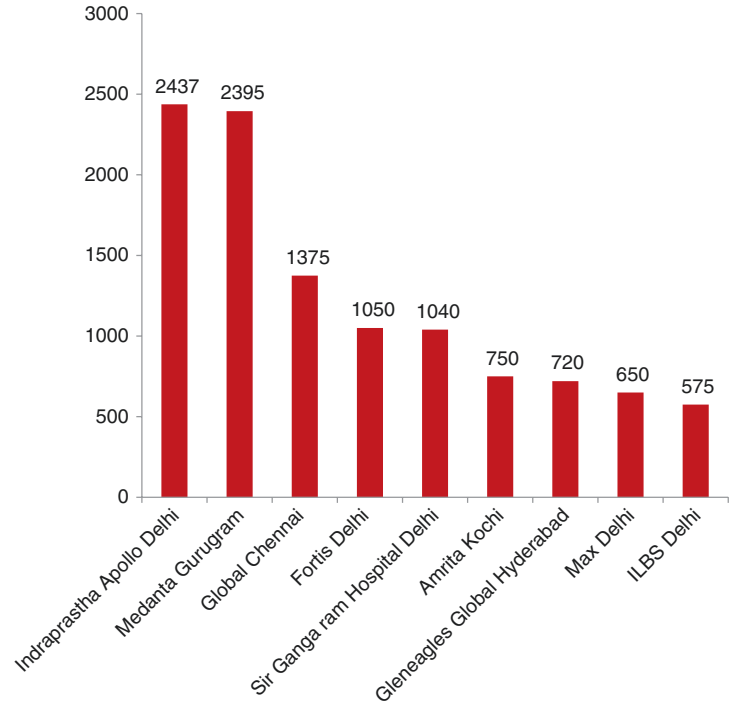

Fig. 1.3 Total liver transplants up to May 2019, Individual Centre Data (>500)

450 done with 12% from deceased donors to 2018 when 1944 were done and 32% were from deceased donors.

However in 2019 after we asked all members of the Liver Transplant Society of India to share their total numbers out of 135 registered centres 40 responded and the individual centre data are provided in Figs. 1.3, 1.4, 1.5, and 1.6.

The activity of hospitals in a single year (2018) is provided in Figs. 1.7, 1.8, and 1.9.

Thus only 4 institutions performed more than 200 in a single year (2018), 11 did 50–100, 30 did 1–50 and 90 others who were registered to perform the operation did not do any liver transplants or did not answer the questionnaire (Fig. 1.10).

When we repeated the same exercise recently in 2020 we only had one reply; perhaps because of the increasing competition or fall in numbers centres are now unwilling to disclose these figures.

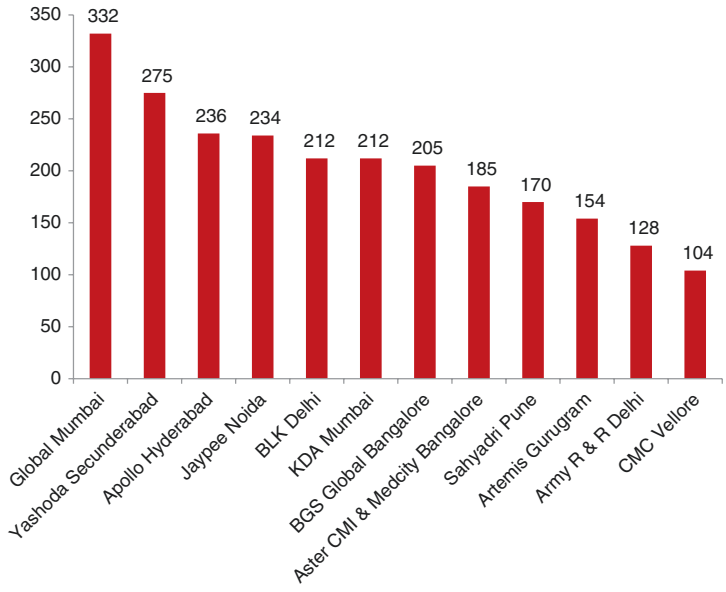

Fig. 1.4 Total liver transplants up to May 2019, Individual Centre Data (100–500)

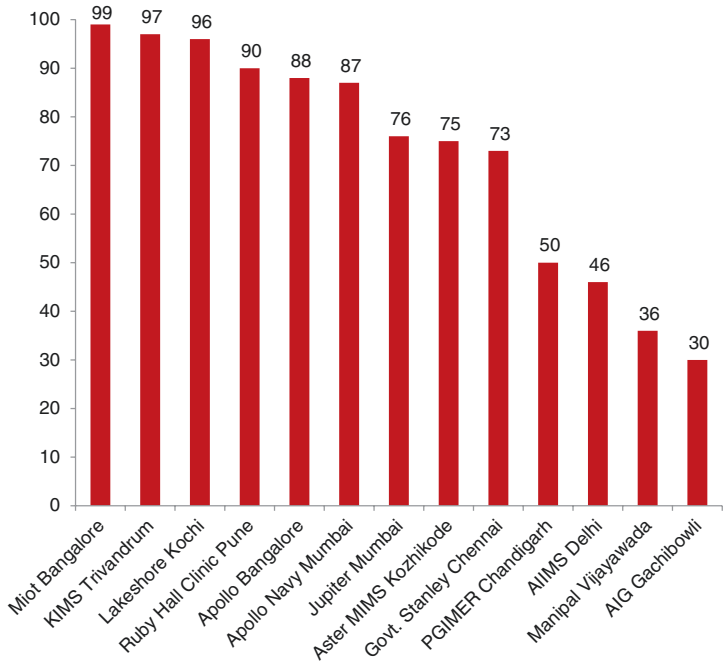

Fig. 1.5 Total liver transplants up to May 2019, Individual Centre Data (<100–30)

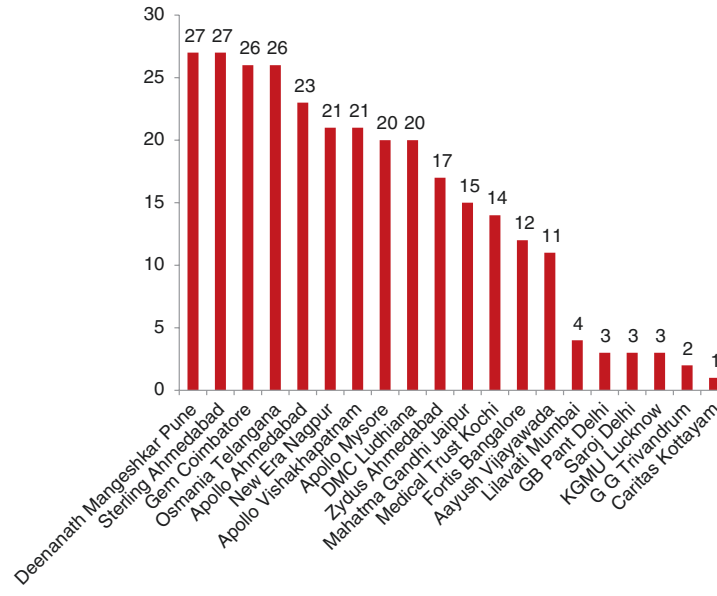

Fig. 1.6 Total liver transplants up to May 2019, Individual Centre Data (<30)

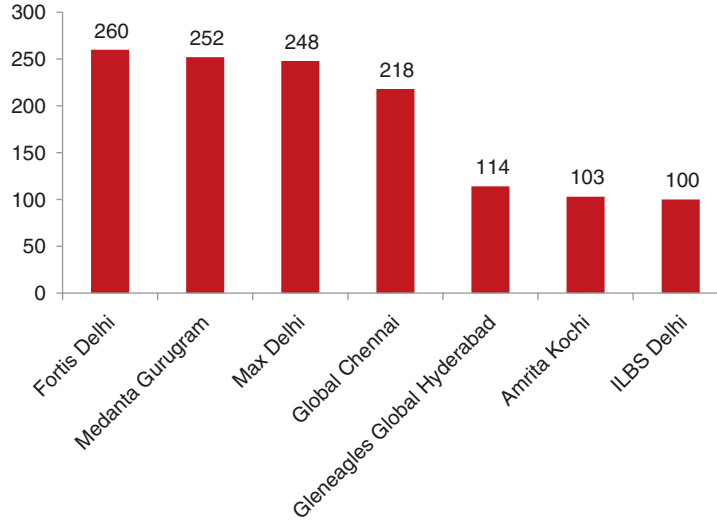

Fig. 1.7 Liver transplants in India in year 2018, Individual Centre Data (>100)

1.6.2 Statewise Distribution

Figure 1.11 shows the distribution of liver transplant centres in India with most in the South, West and North but very few in the Central and Eastern states.

The largest numbers of transplants done in 2018 were in Delhi (1161), which in 2020 has apparently 16 centres, but these were almost all from living donors (Fig. 1.12).

But if the numbers of deceased organ donations are depicted (Fig. 1.13), we will see that most of the activity has been in the Southern and

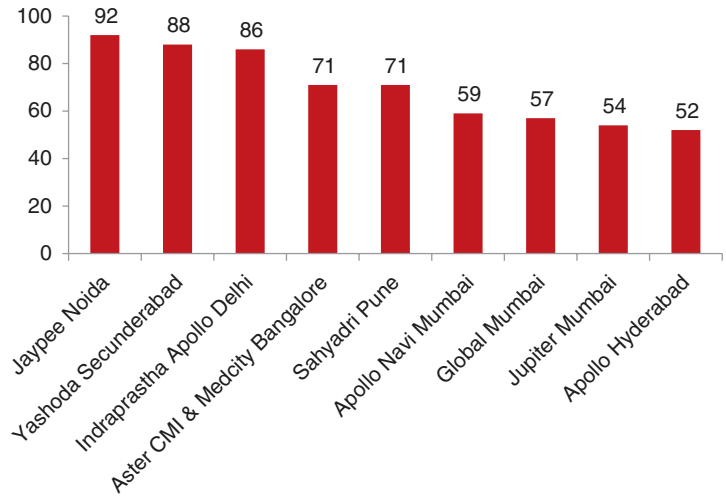

Fig. 1.8 Liver transplants in India in year 2018, Individual Centre Data (<100–50)

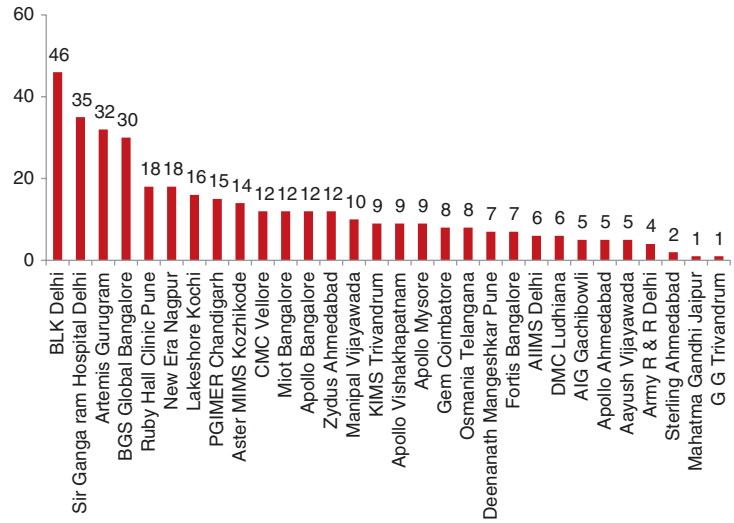

Fig. 1.9 Liver transplants in India in year 2018, Individual Centre Data (>50)

Western states with Tamil Nadu leading the way (Figs. 1.13 and 1.14).

In fact that state has been in the forefront of all deceased organ transplants including the lung, heart, liver and kidney (Fig. 1.15).

1.6.3 The Situation in 2020

The total number of centres registered to perform liver transplants in India is now 135 (compared to a total of 149 in the USA), and this is increasing rapidly as the procedure has become a marker for not only the prestige of a hospital but that of a state. However, it is rumoured that many of the centres although registered have not performed a single transplant or that they have had such bad results that there is little or no continuing activity. Thus the 'star' performing surgeons and their teams are sought after by most large hospital chains by being guaranteed astronomical salaries. Consequently the public sector is now performing only 3% of the transplants not only because it is losing its surgeons to private hospitals but it does not have the committed and dedicated large teams required to collaborate and perform such complex procedures. The cost of a living donor transplant is now anywhere between 16 and 30 lakh rupees.

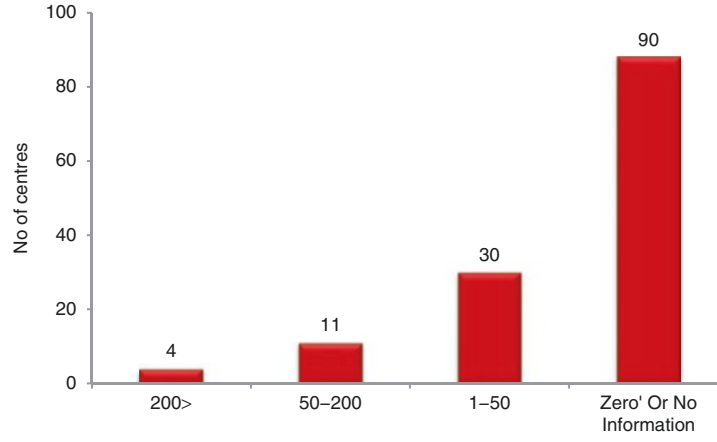

Fig. 1.10 Overview of liver transplants in India in 2018

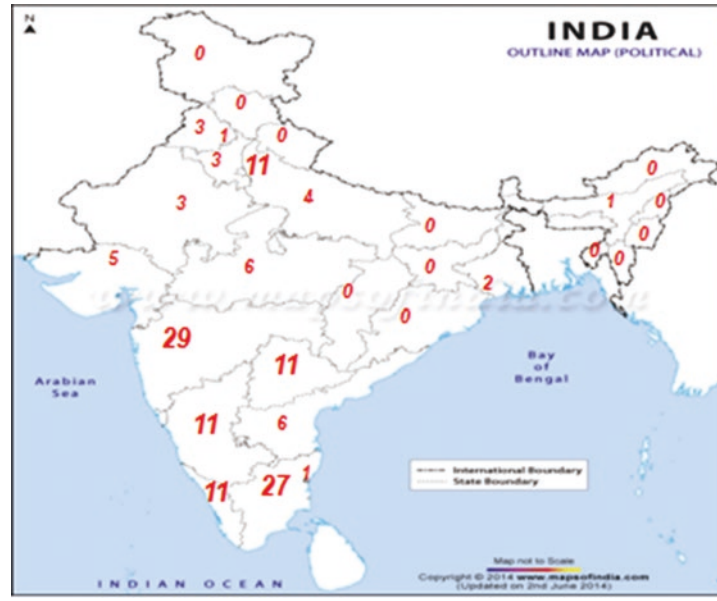

Fig. 1.11 Liver transplant centres

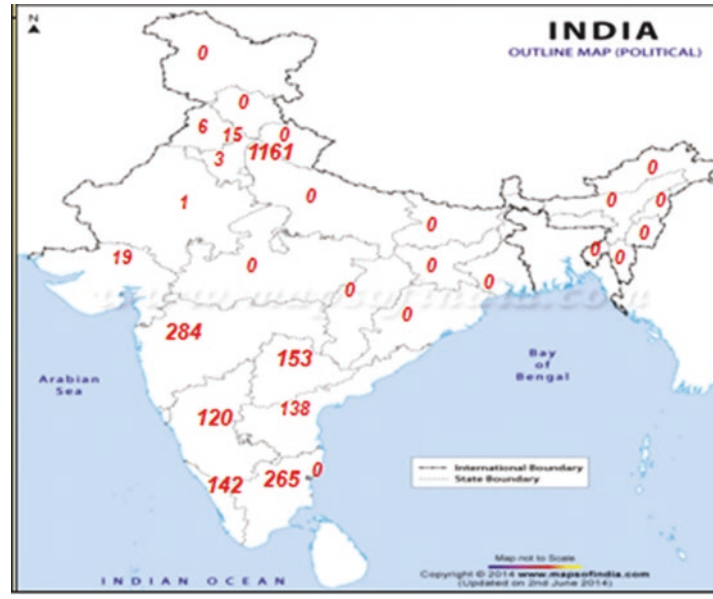

Fig. 1.12 Liver transplant numbers statewise

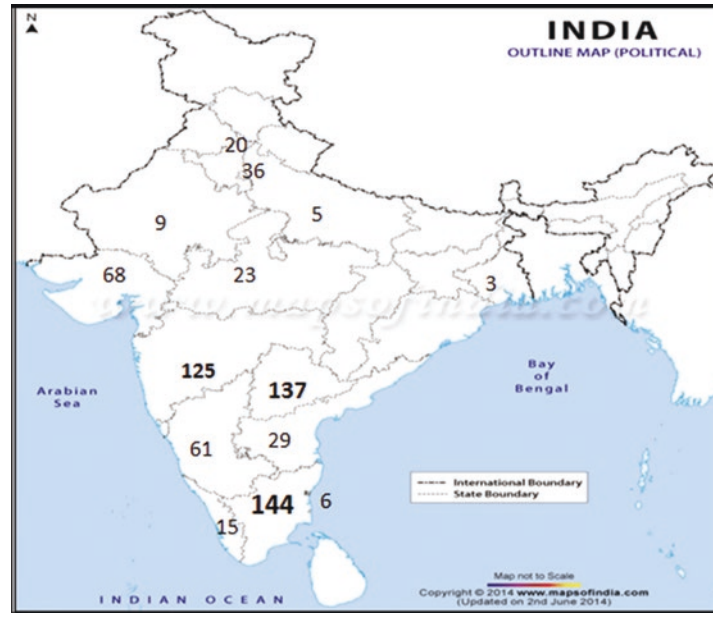

Fig. 1.13 States—deceased donations 2018

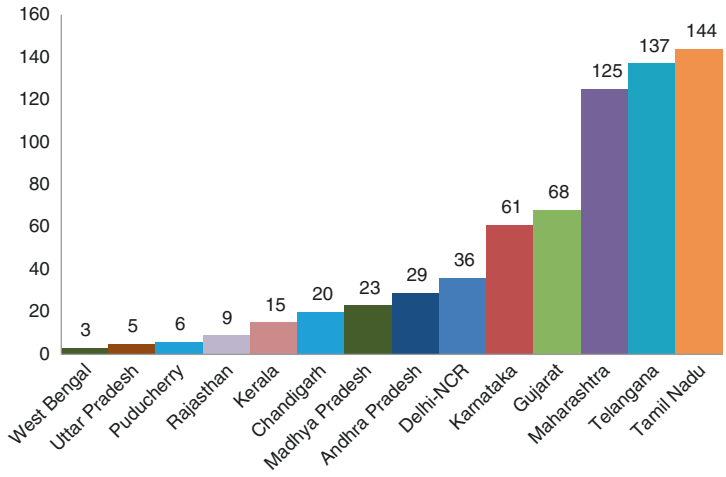

Fig. 1.14 Statewise deceased donor liver transplants 2017

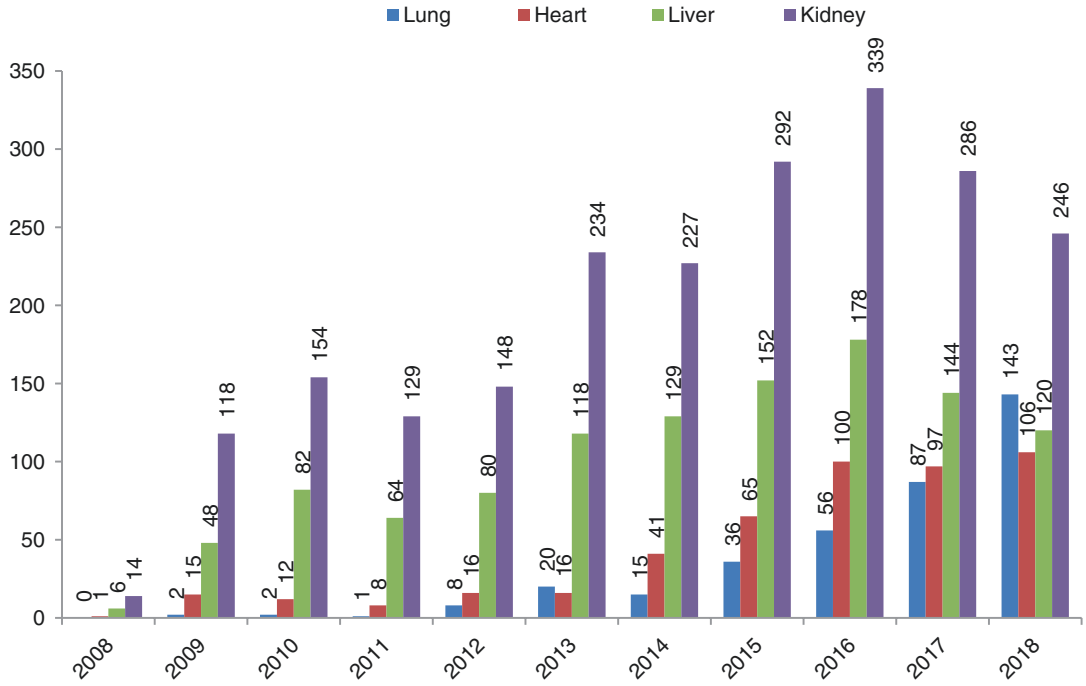

Fig. 1.15 Tamil Nadu deceased organ transplants

1.7 India Vs the World

In 2018 there were a total of 1944 liver transplants performed in India which followed only the USA (8241), China (5149) and Korea (2854). However for the proportions of living donor liver transplants the figures vary considerably from Japan where 87% of transplants were from living donors to 4% and 2% in the USA and UK. In India and South Korea the majority of organs were taken from living donors (68% and 65%). In China although deceased donors are the largest source of organs for transplants most of these are alleged to have been obtained from condemned prisoners. This practice has been decried by the international transplant

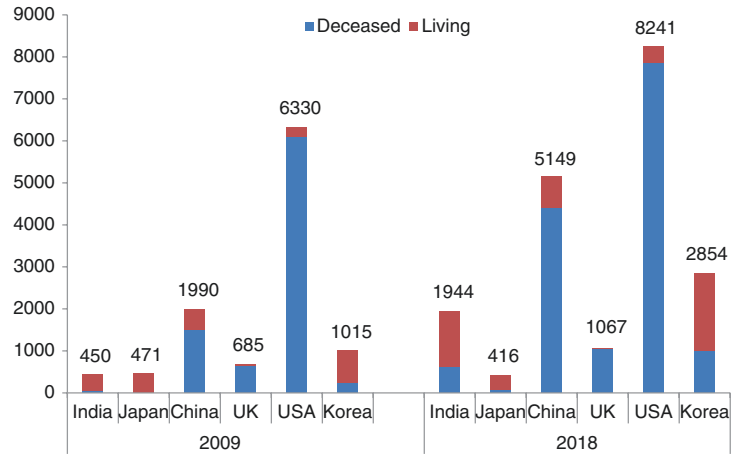

Fig. 1.16 Liver transplants in India vs World (2009 and 2018)

community and is now banned by the Chinese government. Figure 1.16 shows the changes in the numbers of transplants in some selected countries comparing 2009 and 2018.

All have shown increasing numbers except for Japan and what is noteworthy in that is India has probably shown the largest proportional increase of 4.3 times in total with an encouraging rise in the number of deceased donor transplants.

1.8 Concerns

But there are concerns. All the transplant programmes rely mainly on living donors and although deceased donation is increasing in the South and West in the central states, it remains poor in the North and East. This is because of a lack of awareness of the concept of brain death and the benefits of organ transplantation but also perhaps due to an absence of altruism in these areas. Public hospitals have not managed to mount regular programmes and the private sector where profit generation is the main concern this has resulted in large kickbacks to referring physicians, there is immense pressure to increase numbers and many 'marginal' livers which would not be used abroad are transplanted. The system continues to be opaque in that the living donor complications and deaths remain unknown and the results of transplantation are enormously variable ranging from 90-day recipient mortality rates of between 5% and 100%. There is a major gender gap with organ donors being predominantly female and the recipients male. In Tamil Nadu the proportion of females receiving kidney grafts is 23% and livers is 7%. The organ trade continues but it is small and clandestine.

1.9 Recommendations

The first priority should be to improve cadaver donation by strictly enforcing the law especially the 2011 amendments which delinked transplant hospitals from those from which organs could be harvested, enforce mandatory brain death declaration and required request, ensure a transparent and fair organ distribution system and even consider incentives to donor families like free lifetime railway passes. There should be many more centres in the public sector which would lower the cost of the procedure and perhaps improve the gender imbalance.

The dormant Appropriate Authority should collect data on the indications and results of transplantation, help raise public awareness, and encourage the exchange of problems, results and expertise between the private and public sectors. It should also punish unethical practices.

In spite of these problems the results have been gratifying as illustrated in Fig. 1.17.

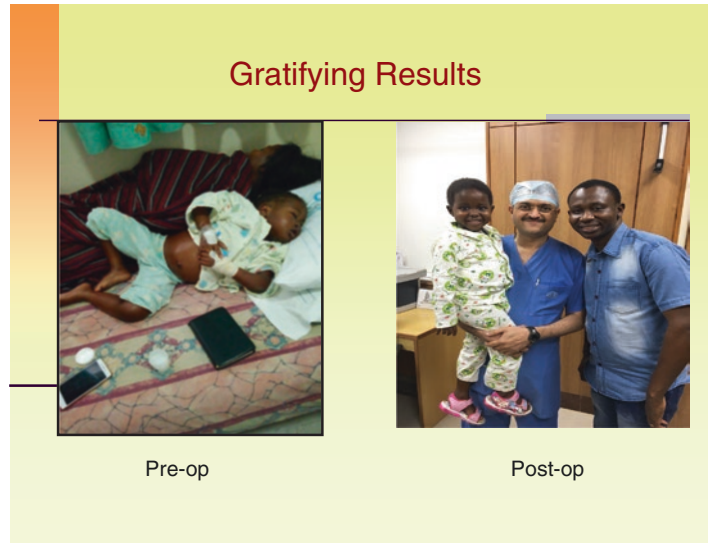

Fig. 1.17 A three-and-a-half-year-old Nigerian girl with a large liver tumour before and after liver transplantation (now well 5 years later)

1.10 Conclusions

Liver transplantation has had a major impact on Indian health care. It has saved thousands of lives of middle-class Indians who could not afford to have the procedure done abroad, it has improved the quality of surgery, anaesthesia, haematology, nephrology, blood transfusion and pathology, the results of the best centres match the world's best and although there are attendant problems these can be solved.

In fact liver transplantation has revolutionised Indian medicine.

Key Points

1. The Transplantation of Human Organs Act of India in 1994 recognised brain death and made the trade in human organs illegal.
2. This allowed liver transplants to be performed in this country.
3. After the first decade when few procedures were done the main impetus came in 2008 when the Tamil Nadu government orders made the declaration of brain death in hospitals mandatory and required doctors to ask relatives for organ donation.
4. There are now 135 centres registered to perform liver transplants in 2020.
5. Most transplants are done in the private sector and are from living related donors.
6. Deceased organ donation occurs in the Southern and Western states but in Delhi, where 54% of the total liver transplants in India are done, the majority are from living donors.
7. India's total liver transplant numbers rank only after the USA, China and Korea.
8. Unfortunately the results regarding indications and operative mortality are opaque and there needs to be closer regulation of the activity throughout the country.
9. Liver transplantation has enhanced the quality and reputation of Indian health care.

Acknowledgements I would like to thank Mr. Parmanand Tiwari for his help in preparing this manuscript.

Part I

Basics Anatomy and Pathophysiology of Liver Disease

2 Physiological Role of Liver and Interpreting Liver Function Tests

Kamal Kajal, Venkata Ganesh, and Sameer Sethi

The purpose of this chapter is to review the anatomy and physiology of the liver as well as provide a brief interpretation of liver function tests. The anaesthetic management of the patient with chronic liver disease requires an in-depth understanding of the altered physiology of the cirrhosis along with pharmacokinetic and pharmacodynamic aspects of therapy. All types of liver surgery can induce transient or permanent injury to the liver, an understanding of which has improved the morbidity and mortality of hepatic transplant recipients and donors over the years.

The importance of the regenerative capacity of the liver cannot be overstressed as this is unique to the liver enabling partial transplants from live donors. This regenerative capacity is well illustrated in the myth of Prometheus [1]. Although potential liver replacement therapies such as Molecular Adsorbent Recirculating System (MARS) are available, these can never take over the extensive functions of this multi-tasking organ. These functions range across metabolic (including detoxification), synthetic, immunologic and homeostatic domains (Table 2.1).

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Table 2.1 Functions of the liver

Metabolic	Synthetic	Immunologic	Homeostatic
Glucose metabolism	Coagulation factor synthesis	Innate immunity	Intravascular homeostasis by acting as a blood reservoir, through renin-angiotensin-aldosterone axis and oncotic pressure regulation via albumin metabolism
Nitrogen metabolism	Procoagulants	Adaptive immunity	Glucose homeostasis
Lipid metabolism	Anticoagulants	Systemic antigen and allograft tolerance	Hepatic and portal blood flow regulation through hepatic arterial buffer response
Heme degradation	Fibrinolytics		
Drug metabolism and detoxification	Antifibrinolytics		
	Plasma protein synthesis		
	Albumin		
	Heme synthesis		
	Endocrine:		
	Steroid hormone synthesis		
	Cholesterol		
	Thrombopoietin		
	Angiotensinogen		
	IGF-1		

2.1 Gross Anatomy of the Liver

The liver derives from the ventral foregut endoderm during the fourth week of gestation [2–4]. Anatomy relevant to anaesthetic and surgical management includes the blood supply and the intrahepatic microscopic architecture.

The afferent blood to the liver is accounted for by both arterial and portal blood. The mean value of O_2-uptake in the liver, related to a blood flow of 110 mL/min/100 g, amounts to 6.08 ± 0.2 mL O_2/min [5]. This comprises 20–25% of the cardiac output. Although in terms of blood flow the portal vein supplies nearly 75% of the hepatic blood and the systemic artery supplies 25%, the oxygen supplied to the liver is equally shared between the two circulations [6]. The biliary tree is however supplied principally by the hepatic artery. The portal blood from the splenic vein brings in the hormones and cytokines from the pancreas whereas the superior mesenteric vein brings in the endotoxins and nutrients from the gut above the lower half of the rectum. In situations of increased portal vein pressure, portosystemic connections open up in areas such as the lower end of oesophagus, rectum, umbilicus, retroperitoneal regions and bare area of the liver. This manifests as dilated veins/varices, bleeding and the shunting of unfiltered blood can manifest as sepsis and encephalopathy.

The venous outflow of the liver is through the three hepatic veins draining directly into the inferior vena cava (IVC) close to the diaphragm and any change in the intrathoracic and right heart pressures or beyond the hepatic vein (such as thrombosis in Budd-Chiari syndrome) can promote congestive injury to the hepatocytes.

Externally the liver can be seen to have the right and the left lobe divided by the IVC and the gall bladder fossa. However surgically, based on the vascular planar anatomy, the liver can be divided into eight segments [7]. Each segment has an afferent pedicle comprised of branches from the portal vein, hepatic artery and bile duct, and each segment drains into an individual tributary of the hepatic vein. The right lobe of the liver has segments V to VIII while the left lobe has slightly complicated segmental division with the true external left lobe comprising segments II and III and the medial portion of this or quadrate lobe is segment IV. The caudate lobe is named as segment I and independently drains into the central hepatic vein.

2.1.1 Hepatic Blood Flow Regulation

Blood flow to the liver is regulated by several intrinsic and extrinsic factors. These pathways work independently of each other.

Intrinsic Mechanisms

1. HABR (Hepatic arterial buffer response): The periportal tissues produce adenosine, the washout rate of which when decreased, as occurs during decreased portal blood flow, dilates the hepatic artery to preserve hepatic blood flow [8, 9]. The reverse also occurs when portal blood flow increases, increasing the washout of adenosine and constricting the hepatic artery. Endotoxemia and splanchnic vasoconstriction can abolish this response [6].
2. Metabolic control: Decrease in the oxygen content or pH of the portal venous blood can increase the hepatic arterial blood flow; postprandial hyperosmolarity can also increase hepatic artery and portal venous flow.
3. Myogenic autoregulation: Vascular smooth muscle stretch during hypertensive episodes promotes vasoconstriction and decreased hepatic arterial flow protecting the liver from the hypertensive episode. The reverse also occurs with vasodilation of the hepatic artery during systemic hypotension. Inhaled volatile anaesthetic agents cause a dose responsive inhibition of this response.

Extrinsic Regulation

1. Neural control: Parasympathetic and sympathetic nerves that course along with the hepatic blood vessels help in regulating the vascular tone. During sympathoadrenal stimulation the blood volume within the hepatic and splanchnic circulation is squeezed into the systemic circulation. The hepatic artery has alpha 1,2 and beta 2 receptors while the portal vein has only alpha receptors [6].
2. Humoral control: Glucagon causes hepatic artery vasodilation whereas angiotensin II causes vasoconstriction of hepatic and portal venous circulation. Interestingly vasopressin raises splanchnic arterial resistance but reduces the portal venous pressures and hence may be preferred in those with portal hypertension.

2.2 Cellular Anatomy of the Liver

The liver is composed of two groups of cells. The majority are parenchymal cells or hepatocytes which are responsible for the metabolic and most of the synthetic functions of the liver. The non-parenchymal cells are chiefly responsible in the liver acting as the immunological gateway especially for the enteric organisms. These include the Kupffer cells, Natural Killer (NK) cells, dendritic cells, T lymphocytes and B lymphocytes as well as the cholangiocytes, the sinusoidal endothelial cells and perisinusoidal pluripotent stellate or Ito cells. Table 2.2 summarizes the functions of these cells.

Table 2.2 Types of cells and their functions in the liver [10, 11]

	Function	Percentage of liver cells
Hepatocytes	• Hepatic regeneration	60–80
	• Detoxification	
	• Protein synthesis and metabolism	
	• Lipid oxidation	
	• Glucose metabolism	
	• Glycogen storage	
Perisinusoidal Ito cells	• Vitamin A and fat storage	5–15
	• Collagen secretion and contractile nature implicates these cells in liver cirrhosis and portal hypertension respectively	
	• Antigen-presenting cells	
Endothelial cells	• Exchange of substrates through fenestrations	15–20
	• Nitric oxide-mediated vascular tone regulation	
	• Antigen-presenting cells	

(continued)

Table 2.2 (continued)

	Function	Percentage of liver cells
Kupffer cells	• Antigen-presenting cells (macrophages)	15
	• Downregulate T cell activation in immune tolerance states	
	• Produce nitric oxide, TNF alpha and other cytokines responsible for ischaemia reperfusion injury	
Dendritic cells	• Antigen-presenting cells	<1
Lymphocytes	• Non-specific targeting of tumour cells and viruses	5–10
NK cells		
T cells	• Cell mediated adaptive immunity and immune memory	
B cells	• Antibody/humoral mediated adaptive immunity and immune memory	
Cholangiocytes	• Comprise the bile ducts	<1

2.2.1 Models of Liver Microanatomy

There are two prevalent models of liver microanatomy. In the lobular model, the terminal hepatic vein (central vein) is at the centre of a hexagonal "lobule" of hepatocytes while the subunits of the portal triad are at the periphery. These units are of individual metabolic capacity representing the fundamental unit of the liver.

In the acinar model, the hepatocytes are grouped in an approximately oval mass with the ends of the long diameter being the central veins of adjacent lobules and the short diameter being defined between two portal triad. This represents the functional microvascular unit of the liver and is based on the blood flow pattern to the hepatocyte. Each acinus is divided into three ill-defined zones, zone 1 being the richly oxygenated periportal, zone 2 intermediate and zone 3 closer to the central veins (Fig. 2.1).

Zone 1 being oxygen rich takes care of the aerobic glucose metabolism and is most resistant to ischaemic stressors. It is also responsible for fatty acid metabolism and urea cycle for ammo-

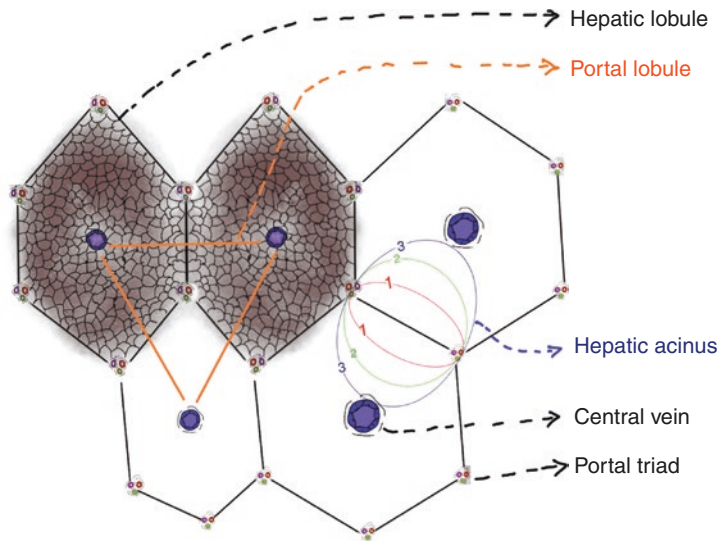

Fig. 2.1 Schematic representation of the microanatomy of the liver showing the hepatic lobule with the portal triads forming the borders of this hexagonal unit with the central vein at the centre of the mass of hepatocytes. The portal lobule is a triangular unit formed by joining three central veins with a portal triad at the centre. The hepatic acinus is a perfusion-based model with the hepatocytes distributed in three oval zones around the short axis of the oval being formed by joining two portal triads and the long axis being bounded by two central veins

nia metabolism. Zone 3 is perivenous and is most susceptible to hypoxia and ischaemia being involved in ketogenesis and drug detoxification. The functions of zone 2 overlap with the other two zones [12–14].

2.3 Liver, the Immunological Gateway

2.3.1 Innate and Adaptive Immunity

The non-parenchymal cells of the liver take part in the immune regulatory function, and both forms of immunity are closely linked within the liver. The hepatic circulation, unlike the systemic circulation, has more of the non-specific innate immune cells, as the major immune function of the liver is to regulate the massive antigen load from the enteric circulation before it reaches the systemic circulation. Hence it acts like an immunological gatekeeper for the body.

The non-specific innate immunity is mediated by the antigen-presenting cells (APC) as well as the NK cells. The APC form a bridge to the T and B lymphocytes that mediate adaptive immunity. These APC include Kupffer cells, dendritic cells, sinusoidal endothelial cells and Ito cells. The NK cells non-specifically target all foreign cells that do not contain self-major histocompatibility surface complex I (MHC-I) such as tumour cells and viruses [15]. These cells directly destroy their targets by secreting perforins that make the target's membrane more permeable and granzymes that lyse the cells internally. Decreased NK cell function has been associated with increased tumour burden [16].

The adaptive immune system is classically comprised of the cell-mediated and antibody-mediated acquired form of immunity which helps in mounting antigen-specific immune response with immunological memory. This memory response serves in quick processing of the antigens that enter the liver from the splanchnic and portal circulation. CD8 T cells can recognize tumour antigens and can help fight against hepatocellular carcinoma as well [17].

2.3.2 Immune Tolerance

Although early cases of transplantation were done exclusively in twins and in closely related individuals, it is a well-known fact that pigs, mice and rats accept unrelated liver transplants without immunosuppressants and even some human recipients are capable of weaning off immunosuppressive therapy [18]. There is also no immune response to the massive load of commensal bacteria in the gastrointestinal tract. This is because the liver manages to balance between acting as an immunological gateway and tolerating the commensal organisms whose antigens have been presented to the liver constitutionally over a prolonged period of time. This function of the liver is termed systemic or oral tolerance and a similar adaptation of the immune system is probably what is responsible for allograft tolerance and transplant success rates [19].

This "tolerogenicity" is thought to be mediated by the constitutive expression of antigens (for example the lipopolysaccharide or LPS of enteric organisms) on the antigen-presenting cells such as the Kupffer cells which tends to downregulate the activity of other antigen-presenting cells over time via TNF alpha and interleukin 10 [20]. This in turn decreases T cell activation [10]. Similar mechanisms underly allograft survival.

2.4 Hepatic Drug Metabolism

Most higher organisms are exposed to a lot of foreign chemical compounds in the environment. Evolution has provided pathways to transmute such xenobiotics to ensure their elimination, onset of action (prodrugs) or termination of effect by altering their susceptibility to excretion.

2.4.1 First Pass Effect

The first pass effect can be defined as the rapid uptake and metabolism of an agent into inactive compounds before it reaches systemic circulation. This phase of drug metabolism greatly reduces the bioavailability of enteral drugs. First pass effect occurs majorly in the liver but also to