



CODEN [USA]: IAJ PBB

ISSN: 2349-7750

INDO AMERICAN JOURNAL OF PHARMACEUTICAL SCIENCES

<http://doi.org/10.5281/zenodo.1318617>

Available online at: <http://www.iajps.com>

Research Article

IMPACT OF CIRRHOTIC LIVER DISEASE: BEYOND SIMPLE MEASURES OF MORTALITY AND MORBIDITY

Muhammad Muneeb¹, Akbar Gohar Abro², Mahesh Kumar Lohano³,
Aatir H. Rajput⁴, Tahir Hanif⁵, Anam Shaikh⁶ and Abid Ali⁷

¹Dept. of Basic Medicine – University of Modern Sciences, Indus Medical College, T.M.K

^{2,3}Dept. of Medicine – Muhammad Medical College, M.P.K

⁴Dept. of Psychiatry – Liaquat University & Sir Cowasjee Jegangir Institute of Psychaitry, Hyd

⁵Central Military Hospital, Kohat

⁶Dept. of Pathology – Ziauddin University, Karachi

Abstract:

Objective: To conduct a multi-dimensional analysis of cirrhotic liver disease, its probable factors, presentation trends, complications and its socioeconomic impact at Liaquat University Hospital.

Methodology: This observational, cross-sectional study comprised of a sample of 99 patients suffering from cirrhotic liver disease at major a tertiary care hospital (namely: Liaquat University Hospital) where patients presented from different parts of urban & rural Sindh. Data was collected using interview based, structured questionnaires from 1st December 2014 to 10th February 2015, after taking verbal informed consent. Data was analyzed using SPSS v. 19.0 and Microsoft Excel 2013.

Results: Nearly the entire sample was suffering from underlying Hepatitis infection with Hepatitis A, B and C being the predominant diagnosed types at 2%, 27.3% and 13.1% respectively. Ascites (62.6%) was the most common symptom while edema (58.6%) shortly followed. Hematemesis (27.3%), Gall/Bile duct stones (20.2%), Un-accounted fractures (13.1%) and Melena (10.1%) were also reported. 89.9% of the respondents had positive blood transfusion history, 31.3% committed frequent alcohol abuse in the past and 19.2% had a family history of live disease, obesity & hemochromatosis. Moreover, majority of the respondents (58.6%) belonged to the lower socioeconomic class.

Conclusion: We conclude on the basis of our findings that Hepatitis, more often than not, is a reason behind cirrhotic disease. Alcohol abuse, un-safe blood transfusions and genetic influence too play a role in disease spread and development. Steps need to be taken to curb the use of un-screened blood for transfusion and alcohol consumption by the public. The cost of treatment at this public sector hospital seems justified but inability to continue work and earn an income during illness, especially among sole earners living in a nuclear family is problematic.

Keywords: Cirrhotic disease, Liver, Hepatitis and Socio-Economic Impact.

Corresponding Author:

Dr. Muhammad Muneeb,

Dept. of Basic Medical Sciences

University of Modern Sciences, Indus Medical College, T.M.K

Email: muhammadmuneebchauhan@gmail.com

Contact Number: +92-331-3676651

QR code



Please cite this article in press Muhammad Muneeb *et al.*, **Impact of Cirrhotic Liver Disease: Beyond Simple Measures of Mortality and Morbidity**., *Indo Am. J. P. Sci.*, 2018; 05(07).

INTRODUCTION:

Chronic disease constitutes a fast increasing burden to society. The World Health Organization (WHO) estimates that 46% of global disease and 59% of mortality is due to chronic diseases. Thirty-five million individuals in the world die each year from chronic disease and the numbers are increasing steadily. [1] The progressive increase in the cost for healthcare in recent decades is expected to continue, in fact accelerate. According to the Office for National Statistics in the United Kingdom, liver disease is now the fifth most common cause of death after heart disease, stroke, chest disease and cancer. [2] However, unlike other major causes of mortality, liver disease rates are increasing rather than declining. A recent UK study showed that mortality rates in Scotland for subjects with cirrhosis have more than doubled for men and have increased by almost half for women. [3]

For hepatologists worldwide, there have never been more challenges faced, yet never more tools available to overcome them. But, stemming the rising tide of global ill health from liver disorders will require the harnessing of resources and long-term strategies through governments, international agencies and those with experience of public health at all levels. Estimated numbers of HBV and HCV infected subjects worldwide are staggering (370 and 130 million subjects respectively) and of the 40 million known HIV positive subjects, 3 million are co-infected with HBV and 4.5 million with HCV [4].

Universal vaccination at birth in high prevalence areas for HBV has been shown to be highly effective in reducing carrier rates in children as well as the incidence of chronic liver disease including hepatocellular carcinoma (HCC). First reported from Taiwan, [5] data is now available from Singapore, China, Malaysia, Thailand, South Korea and elsewhere in the Far East. Vaccination coverage is more than 90% in cities but is thought to be much lower in rural areas. Achieving adequate coverage in rural areas of many high endemic countries is a logistical as well as an economic challenge. Although 182 countries are now including hepatitis B in national immunization programs, [6] large areas of the world with a moderate or high prevalence of HBV remain without immunization strategies. For

instance, most of central Africa and the Indian Subcontinent (although India and Pakistan have recently started a process of implementation) provide little to no immunization, largely due to cost constraints. Even with a cost of less than \$1 for developing countries, a series of 3 doses costs more than the other 6 childhood vaccines. Even with the initiation of infant immunization programs, it will take a long time to reduce the massive adult carrier pools around the world and the severe consequences that arise from such infections.

Another area of major health concern is non-alcoholic fatty liver disease (NAFLD) related to the rising levels of obesity around the world promoted by increasing affluence and more sedentary occupations. Even regions previously exempt, such as the Far East and China, are being affected by adoption of Western lifestyles and habits. Rising rates of alcohol consumption fueled by the same sort of affluence and by greater accessibility to supplies, is adding to the burden of liver disease worldwide. What is perhaps not sufficiently appreciated are the additive effects of steatosis from NAFLD or alcoholic excess on liver disease from other etiologies initiating a more severe and rapid course of disease. The adverse effects of viral co-infection are also of considerable scientific interest and clinical importance.

METHODOLOGY:

This observational, cross-sectional study comprised of a sample of 99 patients suffering from cirrhotic liver disease at major a tertiary care hospital (namely: Liaquat University Hospital) where patients presented from different parts of urban & rural Sindh. Data was collected using interview based, structured questionnaires from 1st December 2014 to 10th February 2015, after taking verbal informed consent. Data was analyzed using SPSS v. 19.0 and Microsoft Excel 2013.

RESULTS:

The staggering rates of hepatitis in Pakistan are becoming common knowledge. The fact was further given validation by our findings that showed that the entire sample was suffering from underlying Hepatitis infection with Hepatitis A, B and C being the predominant diagnosed types. Figure 1 below shows the result in detail.

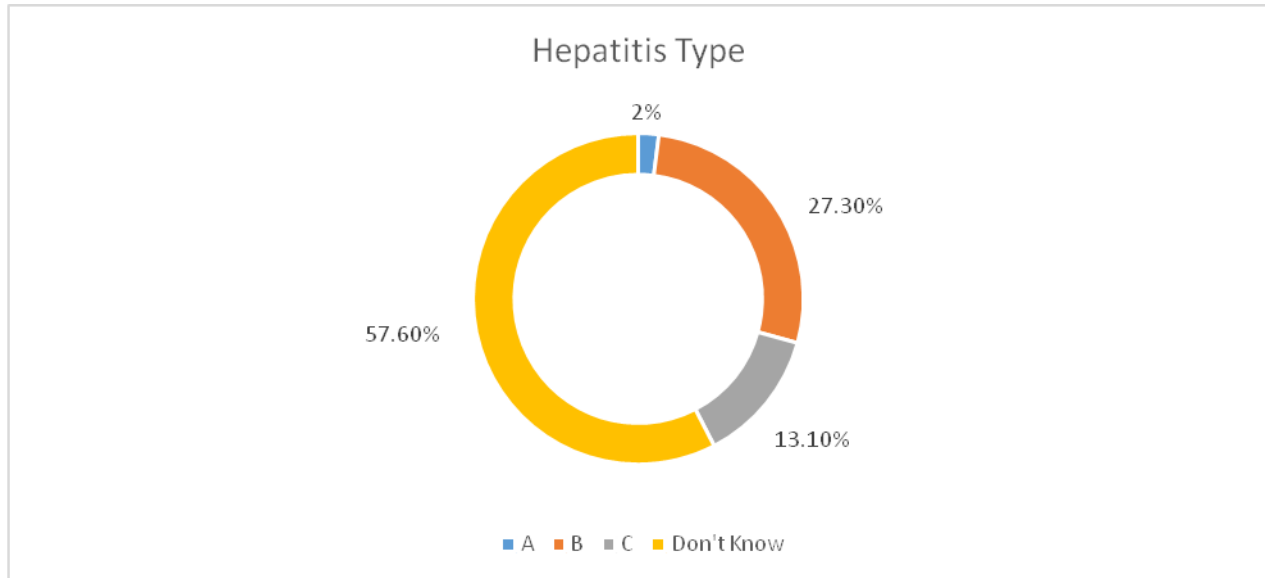


Figure 1: A majority of the sample (57.6%) were suffering from hepatitis like symptoms but lacked test reports and hence we couldn't place them under any particular hepatitis group without testing. The most common diagnosed type of hepatitis infection in our sample was hepatitis type B that stood at 27.3%. This was followed by hepatitis type C that stood at 13.1% in the sample. Third in line was hepatitis A that was reported by 2% of the sample. Other factors that predispose to liver disease were also found present among the patient sample. Positive history of blood transfusion, Habit of alcohol abuse, family history of liver disease, obesity and hemochromatosis.

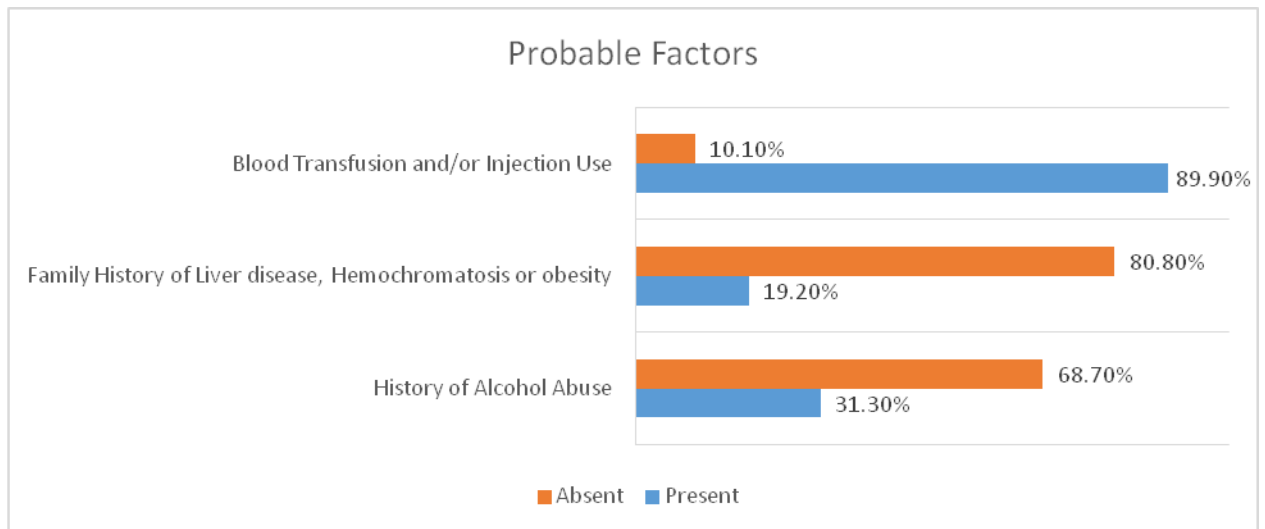


Figure 2: Blood transfusion was positive among 89.9% of the patient sample. Family history of liver disease, obesity and hemochromatosis was present among 80.8% of the patient sample. A history of alcohol abuse was also reported by 31.3% of the patient sample. All factors contribute towards development of liver disease and cirrhosis in particular. However most of the factors are modifiable and can be altered if ample awareness is spread to the vulnerable population.

Ascites (62.6%) was a common symptom while edema (58.6%) shortly followed. Hematemesis (27.3%), Gall/Bile duct stones (20.2%), Un-accounted fractures (13.1%) and Melena (10.1%) were also reported. Figure 3 below shows other complications and compares the results together in detail.

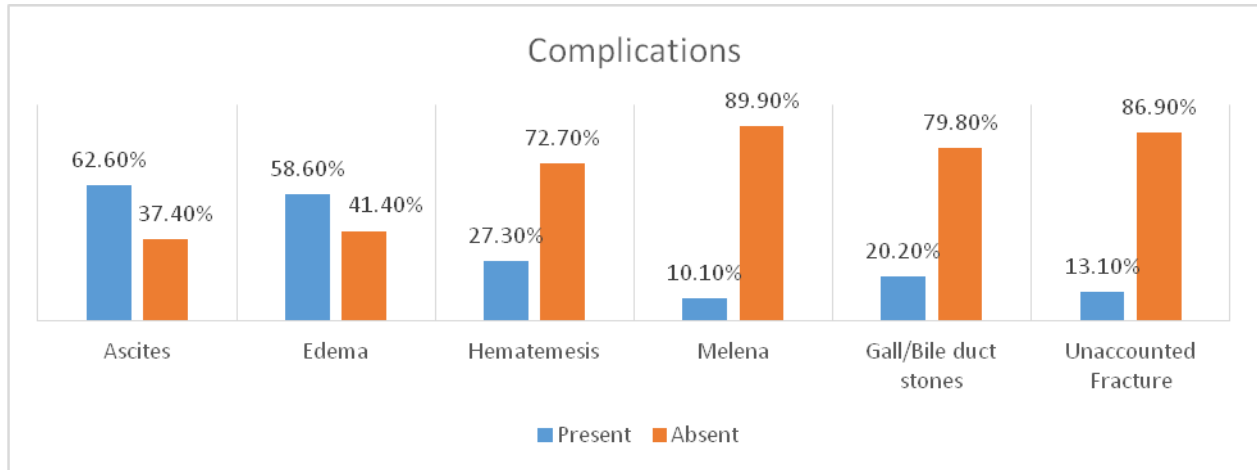


Figure 3: The order of complications in-terms of likelihood of occurrence in the patient sample is as follows. Ascites is the commonest problem, followed by Edema, Hematemesis, Gall/Bile duct stones, un-accounted fractures and lastly melena. The results may vary in different socioeconomic and demographic settings. Time may also contribute to changes.

58.6% of the respondents belonged to the lower socioeconomic class, 40.4% belonged to the middle socioeconomic class while only 1% belonged to higher socioeconomic class. 52.5% of the respondents lived in a joint family setting with multiple sources of income while 47.5% lived in separate nuclear families and were often the sole income earners. The mean monthly income of the sample was PKR 27677 while the mean cost utilized since start of treatment was admittedly PKR 13273. The income and cost details are further elaborated by figure 4 (left) and figure 5 (right).

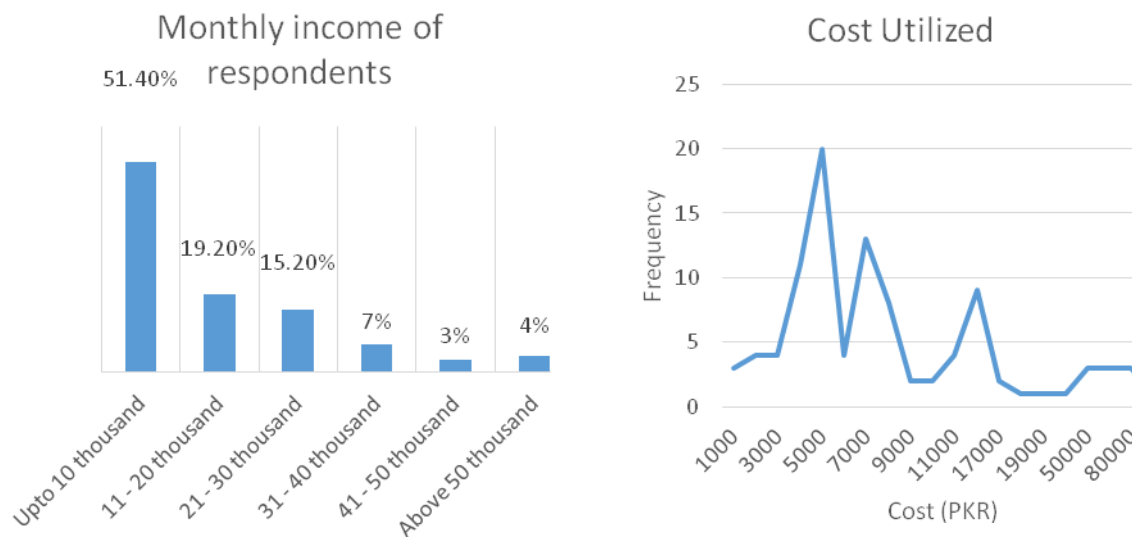


Figure 4: More than half the population (51.4%) earned lesser than the required expenditure of cirrhotic liver disease.

The rest of the 48.6% of the patient sample earned more than the mean cost of treatment to varying extent but whether or not they earned enough to support their other expenditures remains a worrying question especially when the cost of living and the cost of treatment is increasing day by day.

Figure 5: The cost utilized is variable in each case and depends a lot upon the severity of disease, the quality of medicine used and the type of surgical approach (if any) adopted. Comorbidities also play a valid part. The mean cost is PKR 13272 but the standard deviation is extremely high. Ranging from PKR 1000 for new patients to PKR 80,000 in chronic patients suffering from many years.

The respondents had been admitted to the hospital a mean number of 3 times. Cirrhotic disease had forced more than half the patient sample to quit work. The statistics are further elaborated in the figure 6 (right) and figure 7 (left) below.

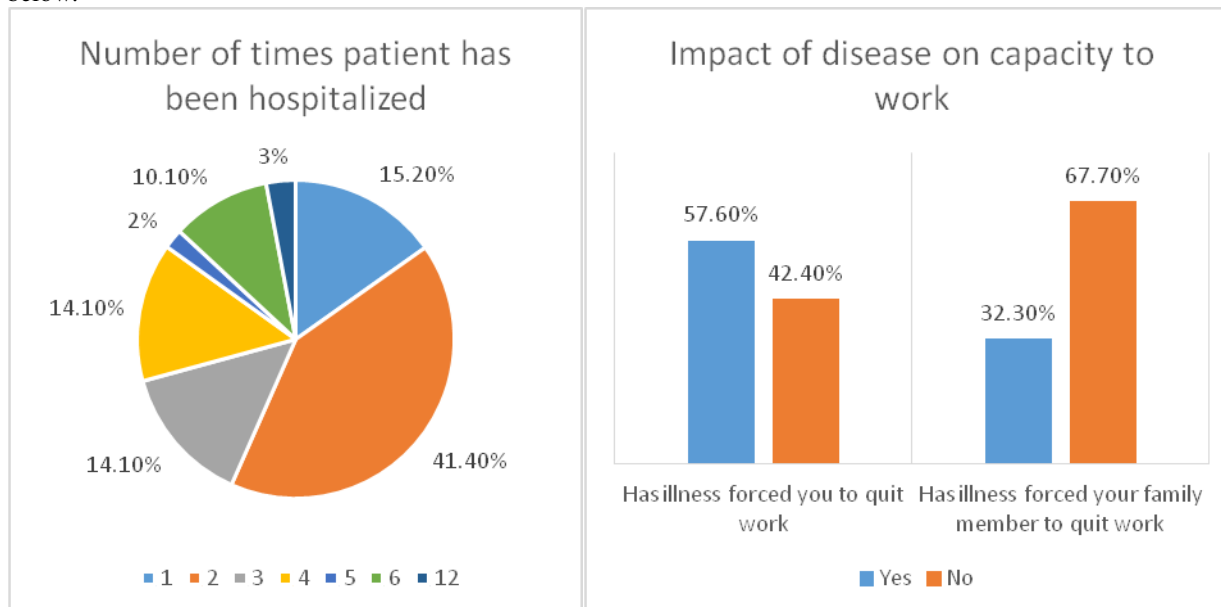


Figure 6: The patient hospitalization mean too carried a high standard deviation and ranged from one to 12 times. With the greatest percentage (41.4%) of patient sample being hospitalized 2 times. It is important to note that the cost of treatment multiplies, each time the patient gets hospitalized.

Figure 7: The disease rendered a large percentage of the patient sample (57.6%) unable to work. The family member, especially the primary caretakers too had their abilities to work compromised due to patients disease and 32.3% had to leave work and stay home or at the hospital with the patient to provide care.

DISCUSSION:

The traditional factors that lead to cirrhosis were in abundance in the patients presenting at Liaquat University Hospital. Obesity, however was uncommon in our sample even though its significance in international literature is significant. Although only a small percentage, possibly 5% of those with severe hepatic steatosis, will progress over many years to significant fibrosis and even cirrhosis,[7] the sheer size of the numbers falling into the overweight/obese category with a body mass index (BMI) of > 25 is the basis for the description of a new epidemic of cirrhosis in the west. One study in the United States using proton magnetic resonance spectroscopy showed that 1 in 3 adults had steatosis as defined by a hepatic triglyceride content of >5.5%; a finding which if applied to the whole population would translate to more than 60 million potential sufferers from NAFLD.[8] In Italy, where the population is usually considered to be at low risk, a recent cohort study showed 1 in 4 or 5 to be suffering from NAFLD.[9] Figures are lower in China and Japan where incidence of the disease is 15% and 14% respectively,[10, 11] but these numbers will only worsen with the increasing adoption of a Western lifestyle. Indeed, in China the number of obese

subjects has doubled in 10 years. The first comprehensive national survey in 2004 on Diet, Nutrition and Disease found that an estimated 200 million of the Chinese population of around 1.3 billion were overweight. Twenty million had diabetes and 160 million hypertension.[22] In the UK, recent surveys have shown 25% of the population to be obese. Most worryingly are the numbers of children falling into this category with documented instances of NAFLD leading to severe hepatic fibrosis even cirrhosis in the late teens.

In the context of a high BMI, NAFLD is correlated particularly with central (truncal) obesity and is part of what has been termed the metabolic X syndrome. This includes hypertriglyceridemia, decreased high density lipoprotein cholesterol, hypertension and most importantly insulin resistance. The latter is of central importance in the pathogenesis of NAFLD with progression to impairment of glucose tolerance in many cases.[13]

The presence of steatosis in the liver is increasingly recognized as an additional risk factor for the development of additional injury. Excess body weight in subjects with heavy alcohol consumption

markedly increases the severity of steatosis and is a risk factor for the development of acute alcoholic hepatitis and cirrhosis. [14, 15] Similarly, in hemochromatosis, the odds of having liver fibrosis increase by 3.9% when steatosis is present. [16] The pathogenesis and effects of steatosis have been extensively studied in chronic HCV infection. Usually, if only to a slight or moderate degree, the presence of steatosis and insulin resistance is correlated with central obesity, except in genotype 3 infections where there may be an additional viral induced mechanism. [17] An association with the metabolic syndrome is sufficient explanation for the many reports describing a significantly increased prevalence of type 2 diabetes mellitus in chronic HCV hepatitis. In a case-controlled study of patients without cirrhosis on liver biopsy, a third of the HCV infected patients had type 2 diabetes mellitus, a remarkably increased prevalence not found in patients with chronic hepatitis B or matched controls.[18] The presence of steatosis and particularly the progression of insulin resistance to diabetes mellitus adversely affect the course of chronic hepatitis C leading to an increase in steatohepatitis and higher annual rates in the progression of fibrosis.[19–21] In patients with non-genotype 3 infection, the presence of steatosis is a predictor of treatment failure with antiviral agents. Obesity appears to be independently associated with the reduced response rates, though as the majority of cases also have steatosis, the inter-relationships are difficult to separate. [22]

Developing countries are experiencing rising levels of alcohol consumption and alcoholic liver disease is becoming even more of a global problem. The rising mortality rates from alcoholic cirrhosis already referred to in the UK can be correlated with an increase in consumption. The latter in turn is inversely related to the curve relating price of alcohol to income (Fig. 3). Another important factor is the greater number of outlets selling alcohol as well as the longer licensing hours recently introduced in the UK.[23] Of particular concern is the younger age at which people are beginning to drink. The number of 14-year-old children buying alcohol illicitly, ie, under the age of 18, in the UK has doubled over the past 15 years. Eleven million adults are estimated to binge drink regularly in the UK, and there are an increasing number of hospital admissions from acute alcoholic hepatitis. Alcohol abuse has also been shown to be an adverse risk factor in the progression of severe fibrosis/cirrhosis from HCV infection. Interactions between alcohol consumption and hepatitis B and C infections are also seen in the context of primary HCC. Although this tumor will develop in cirrhosis

of any etiology, hepatitis B and alcohol account for 80% of cases worldwide. Epidemiological studies have also shown a rising incidence in the West. A recent study on the influence of alcohol and other non-viral risk factors in HCC cases as compared to cirrhotic controls showed that the risk of HCC was increased 6-fold for alcohol, 5-fold for tobacco and 4-fold for obesity. Dose-dependent relationships were demonstrable between alcohol, tobacco exposure and the risk of HCC with significant interactions between the three factors as evidenced by synergistic indices of >1. [24]

Interestingly, there is evidence that the frequency of intrahepatic cholangiocarcinoma (IHC) (a tumor seen considerably less frequently than primary HCC in the West) is also increasing. A recent case-controlled study of all patients with IHC aged 65 or older identified during 1993-1999 in population based registries in the United States (equivalent to 14% of population) identified a number of significant risk factors.[25] These included nonspecific cirrhosis (adjusted odds ratio 27.2), alcoholic liver disease (7.4), hepatitis C (6.1), HIV (5.9), and diabetes (2.0)

Another challenge and again one with global implications, is organ donation. There is a failure to keep up with the need for transplantation of those with end-stage liver disease. As a result, a substantial number of patients are dying on waiting lists worldwide before an organ becomes available for them. Among the various approaches being pursued to increase the number of available grafts is the use of marginal donors, namely those in which the cadaver graft has been adversely affected by factors such as pressor requirement, hypernatremia, and (relevant to this paper) hepatic steatosis. Steatosis has been shown to increase sensitivity of liver to ischemic and reperfusion injury and the use of marginal grafts and those obtained from non-heart beating donors are accompanied by a higher incidence of primary nonfunction and early graft impairment as well as a poorer long-term outcome.

Estimates of steatosis in cadaver organ grafts are staggeringly high and range from 37%-51% with 21% having levels greater than 30%, at which point graft function can be severely affected.[26, 27] In grafts from living donors who by selection represent a relatively healthy group, steatosis of some degree is found in one third to one half with 5%-15% of cases having more than 30% of hepatocytes affected.[28, 29] The steatosis, as in other situations, is closely correlated to BMI. Overall, this means that a substantial number of grafts, whether from cadaver or from living donor, cannot currently be used. Impaired

rates of hepatic regeneration with steatosis can also have an impact on the recovery of the living donor.[30] According to a recent systematic review there have been an estimated 12-13 donor deaths following adult living donor liver transplantation.[31] With donation of the right lobe carrying greater risks for the donor than that of the left lobe, a good argument can be made for greater use of left lobe grafts, particularly now that graft congestion which is the basis of the small-for-size syndrome, can be controlled by restricting arterial inflow and ensuring an adequate hepatic outflow.[32]

The value of regulatory interventions by governments in maximizing organ donation can be substantial. Spain sets the greatest example where the cadaver organ donation rate in 2005 was 35.1 per million population, compared with a miserable 12.8 per million in the UK, and corresponding liver transplant rates of 24.3 and 10.3 per million, respectively. The Spanish system is based on a statutory responsibility placed on hospital authorities to maximize organ donation with a senior authority appointed to oversee its implementation. Its introduction into Australia and South America was also successful in raising donation rates. Another example of effective organizational change brought about by government action comes from Italy where organ donation was increased from 15.3 to 21.1 per million population over a 2-year period with corresponding increases in liver transplantation rate from 12.6 to 18.2 per million.[33]

The pace and technological advances of modern day research are such that many of the previously intractable problems encountered in liver disease are being unraveled. Techniques recently reported for culturing the HCV virus should lead to rapid advances in the production of an effective vaccine, and more effective antiviral drug regimes are in the pipeline. Hepatologists can also do much more for individual patients in terms of better managing the major complications of ESLD, ascites, variceal bleeding, and hepatic encephalopathy. Also, perhaps with albumin dialysis we are at last getting nearer to developing an effective liver support device. [34, 35]

CONCLUSION:

We conclude on the basis of our findings that Hepatitis, more often than not, is a reason behind cirrhotic disease. Alcohol abuse, un-safe blood transfusions and genetic influence too play a role in disease spread and development. Steps need to be taken to curb the use of un-screened blood for transfusion and alcohol consumption by the public. The cost of treatment at this public sector hospital

seems justified but inability to continue work and earn an income during illness, especially among sole earners living in a nuclear family is problematic.

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