ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 04 | April - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

PREVALENCE OF NAFLD AMONG HEALTHY LIVER DONORS

Gastroenterology

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ABSTRACT

NAFLD is hepatic pandemic of the twenty first century, being leading cause of chronic hepatic disease in western world. We did a cross sectional study to find out prevalence of NAFLD among prospective healthy liver donors at a tertiary care hospital at New Delhi, India over a period from June 2014 to March 2016. 124 apparently healthy prospective liver donors were selected. Exclusion criteria were set to exclude all those who had significant history of alcohol intake (defined as greater than 30g/day for men and greater than 20g/day for women over last two years), Hepatitis B or C infection, severe surgical weight loss or emaciation, Obstructive Sleep Apnea, Celiac disease, history of drug intake known to cause hepatic steatosis. Out of 124 prospective liver donors included in this study, 29 (23%) donors were found to have fatty liver on USG abdomen; 38 (31%) donors had fatty liver on unenhanced CT of the abdomen (LAI of ≤ 5 HU); 61 (49%) donors had fatty liver on magnetic resonance.

KEYWORDS

liver, steatosis, fatty liver, magnetic resonance spectroscopy

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the hepatic pandemic of the twenty first century, being the number one cause of chronic hepatic disease in the western world.[1] The diagnosis of NAFLD is usually established with radiological imaging techniques or by the presence of ≥ 5% hepatic fat accumulation on liver biopsy in the absence of other recognized causes of fatty liver. NAFLD is histologically further categorized into non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL is classically defined by the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes. NASH is defined as the presence of hepatic steatosis with evidence of inflammation and hepatocyte injury (ballooning) with or without fibrosis.[2]

The assessment of hepatic steatosis is essential for living liver donor selection because significant hepatic steatosis can affect postoperative outcomes in the donor. The utilization of steatotic living liver donors has been highly variable among surgeons in different medical centers and in different countries. Therefore, an accurate diagnosis of hepatic steatosis and objective quantification of this condition is of paramount importance for the clinical decision making regarding liver donation by live donors, the safety of the living donor, and for estimation of recipient prognosis. The maximum amount of steatosis for a safe LDLT has not been established although values ranging between 30% and 60% are mentioned in the literature.[36]

Subject And Methods

This was a prospective cross sectional study carried out in the departments of Medical Gastroenterology and Liver transplantation in a tertiary care hospital at New Delhi over a period from June 2014 to March 2016.

The study population was based on prospective liver donors. These prospective liver donors underwent pre liver donation work up as per existing protocol followed at IAH (The pre donation work up protocol followed at IAH-Delhi is appended at the end –Appendix A). We excluded donors who had:

- Significant history of alcohol intake (defined as greater than 30g/day for men and greater than 20g/day for women over last two years).
- Hepatitis B or C infection.
- Severe surgical weight loss or emaciation.
- Obstructive Sleep Apnea.
- Celiac disease.
- History of drug intake known to cause hepatic steatosis.

After explaining to the participants the purpose of the study and obtaining a valid informed consent (Consent proforma attached as Appendix B) the demographics, examination findings, results from blood investigations, radiological investigations and liver biopsy findings were noted. Testing for fatty liver was done with:

A) **USG abdomen:** USG abdomen for assessment of hepatic fat was done by sonologists blinded to the data about laboratory investigations. Grading of steatosis was based on visual analysis of the intensity of the echogenicity. When the echogenicity was just increased, it was graded as grade I; when the echogenic liver obscured the echogenic walls of portal vein branches, it was graded as grade II and, when the echogenic liver obscured the diaphragmatic outline, it was graded as grade III fatty infiltration.[7]

B) **CT Abdomen:** Imaging protocol on MDCT consisted of obtaining non-contrast images through the liver parenchyma, followed by CT angiography in the arterial, portal, and hepatic venous phases. CT examination was done on 64-row MDCT (Aquilion; Toshiba Medical Systems, Tokyo, Japan). Low-dose, unenhanced CT (80 kV, 100 mAs with dose modulation, collimation of 128 × 0.625, 10-mm section thickness) were performed. For each case, the hepatic attenuation was measured by means of a random selection of circular regions of interest (ROIs) on both lobes. The ROI values were averaged as a mean hepatic attenuation. To provide an internal control, the mean splenic attenuation was also calculated by averaging three random ROI values of splenic attenuation measurement. The largest possible ROI (size range: 200-400 mm2) were selected to represent splenic parenchymal attenuation. The liver attenuation index (LAI) was derived from the difference between mean hepatic attenuation and mean splenic attenuation and was used as a parameter for prediction of the degree of macrovesicularsteatosis. A difference in attenuation of the liver and spleen of 10 HU was taken as normal.[8]

C) **Magnetic Resonance Spectroscopy:** MR examinations were performed in supine position on 3.0 T MR Scanner (Achieva; Philips, Netherlands) with a single-channel body coil and a phased-array sense torso coil. The commonly used field of view (FOV) for MRI studies was 450 × 340 mm. A three-plane localization imaging sequence was

performed at the beginning of the examination. Forin vivo 1H-MRS, a $20 \times 20 \times 20$ mm^3 voxel was placed in the right hepatic lobe (Couinaud segments V-VIII), avoiding major blood vessels, bile ducts, or liver edges seen on the localization images, and was shimmed automatically. Hepatic fat content was measured by 1H respiratory-gated stimulated-echo acquisition mode (STEAM) spectroscopy by using a repetition time of 2000ms. After a single Pre-acquisition excitation pulse to balance T1 saturation on subsequent excitations, five stimulated-echo acquisition mode spectra were acquired at echo times of 15, 20, 25, 30, and 35ms in a 72 s free breathing technique with respiratory triggering of excitation. This echo time range enabled reproducible T2 estimation while minimizing the confounding effects of fat-peak J coupling. An average display spectrum of the five different TE spectra was obtained and areas of water and the three major fat spectral peaks (0.9, 1.3, and 2.1ppm) were measured.

Hepatic fat fraction (HFF) was calculated and was expressed as:
HFF (=lipid peak area/ (water peak area + lipid peak area) × 100).

A single experienced observer analyzed the spectra using MRI vendor supplied standard MRS post-processing software package followed by an in-house developed method to address the inherent effect of spin relaxation on metabolite estimation.[9]

Liver biopsy was not done in all prospective liver donors included in this study. Consequently, Magnetic resonance spectroscopy (MRS) was used as gold standard against which the accuracy and predictive values of other radiological diagnostic modalities like USG abdomen and non-contrast CT abdomen was compared. There is a lot of data available in literature suggesting MRS is highly sensitive and specific for estimation of hepatic fat as compared to liver biopsy. Some studies have found MRS to be better than liver biopsy in the estimation of hepatic fat.[10]

D)**Liver Biopsy:** Ultrasound guided 18 gauge percutaneous biopsies of the right lobe were performed by a radiologist in those donors in whom biopsy was deemed to be essential (Low LAI values, high hepatic fat on MRS or transaminitis). Samples were fixed in 10% formalin and processed routinely. Two to three tissue cores were obtained, each averaging 1.2 cm in length. Six connective tissue sections of 4-micron thickness were taken and stained with hematoxylin and eosin (H&E). Biopsies were evaluated by an experienced hepatic pathologist blinded to clinical characteristics of patients. Fat was graded quantitatively employing a 20X objective according to the total percentage of hepatocytes involved over the six tissue levels. We followed histological scoring system for non-alcoholic fatty liver disease (NAFLD).[11] In the present study, liver biopsy for the assessment of hepatic fat was only done in twenty five prospective liver donors. As per the donor evaluation policy followed at our hospital, liver biopsy is only done in those prospective liver donors who have low LAI values on CT (LAI <0HU) or are found to have hepatic fat of more than 20% on MRS or have transaminasemia.

RESULTS AND OBSERVATIONS

1. Age And Sex Distribution Of Prospective Liver Donors

A prospective, observational, cross sectional study was carried out from June 2014 to March 2016. In this study, a total of 124 apparently healthy prospective liver donors were included. Out of these 124 prospective donors, 73 (59%) were male and 51(41%) donors were female. Table 1 shows the sex distribution of prospective donors included in this study.

Table 1: Sex Distribution Of Prospective Liver Donors.

Sex	Count	% age
Female	51	41%
Male	73	59%
Grand Total	124	100%

Table 2 shows the age distribution of the prospective liver donors included in this study. Mean age of prospective liver donors was 31.71 years. Mean age of male donors was 30.47 years and mean age of female donors was 33.49 years. Majority of the donors (68%) were in the age group of 21-40 years. 10% donors were less or equal to 20 years of age. 5% donors were above 50 years of age.

Table 2: Age Distribution Of Prospective Liver Donors.

Age (years)	Count	%
≤ 20	12	10%
21-30	56	45%
31-40	28	23%
41-50	22	18%
> 50	6	5%
Grand Total	124	100%

2. Prevalence Of Fatty Liver Among Prospective Liver Donors On USG Abdomen

Out of 124 prospective liver donors included in this study, 29 (23%) donors were diagnosed to have fatty liver on USG abdomen while as 95 (77%) did not have fatty liver on USG abdomen. Prevalence of fatty liver among prospective liver donors on USG abdomen is shown in table 3.

Table 3: Prevalence Of Fatty Liver On USG Abdomen

USG abdomen	Count	%
No Fatty Liver	95	77%
Fatty Liver	29	23%
Grand Total	124	100%

3.Prevalence of fatty liver on Non Contrast Computerised Tomographic Scan of the Abdomen (NCCT abdomen) using Liver Attenuation Index (LAI)

Out of 124 prospective liver donors, 38 (31%) donors had CT LAI ≤5 HU (fatty liver) while as 86 (69%) donors had CT LAI >5HU (no fatty liver). Prevalence of fatty liver amongst prospective liver donors is shown in table 4.

Table 4: Prevalence Of Fatty Liver On CT LAI

LAI	Count	%
≤ 5	38	31%
> 5	86	69%
Grand Total	124	100%

4.Prevalence of fatty liver on Magnetic Resonance Spectroscopy (MRS) among prospective Liver donors

Out of 124 prospective liver donors, 61 (49%) donors had hepatic fat ≥ 5% on Magnetic.

Resonance Spectroscopy (MRS) while as 63 (51%) donors had hepatic fat < 5%. Prevalence of fatty liver on MRS in prospective liver donors is shown in table 5.

Table 5: Prevalence Of Fatty Liver On MRS

MRS	Count	%
< 5%	63	51%
≥ 5%	61	49%
Grand Total	124	100%

Comparison of prevalence of fatty liver on USG abdomen, CT LAI and MRS among prospective liver donors is shown in figure 1.

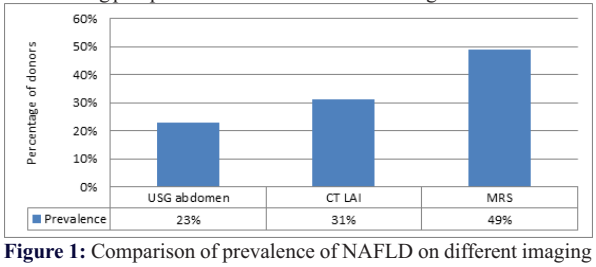

Figure 1: Comparison of prevalence of NAFLD on different imaging modalities among prospective liver donors

5. Prevalence Of Fatty Liver On Liver Biopsy (Percentage fat ≥ 5%)

Liver biopsy was done only in twenty five prospective liver donors, who either had low LAI value (LAI< 0HU) on CT abdomen or hepatic fat > 20% on MRS or unexplained transaminitis. Consequently, out of 25 prospective liver donors in whom liver biopsy was done, hepatic fat ≥ 5% on liver biopsy was found in 22 (88%) and hepatic fat < 5% was present in only 3 (12%) prospective donors. Hepatic fat distribution on liver biopsy is shown in table 6.

Table 6: Hepatic Fat Distribution On Liver Biopsy

LIVER BX	Count	%
< 5%	3	12%
≥ 5%	22	88%

Grand Total	25	100%

DISCUSSION

Diagnosis of NAFLD among prospective liver donors is of utmost importance. The development of primary graft dysfunction, early allograft dysfunction, poor overall graft survival and other complications have been reported in recipients of steatotic grafts in liver transplantation.[12 13] An accurate diagnosis of hepatic steatosis and objective quantification of this condition is thus of paramount importance for the clinical decision making regarding liver donation by live donors, the safety of the living donor, and for estimation of recipient prognosis.

Prevalence Of Non Alcoholic Fatty Liver Disease (NAFLD) Among Prospective Liver Donors

Out of 124 prospective liver donors included in this study, 29 (23%) donors were found to have fatty liver on USG abdomen. From India, community based studies report prevalence of NAFLD on USG abdomen to range between 16.6% to 32%.[14 17] Singh et al. and Bajaj et al. in hospital-based studies reported a prevalence of 24.5% and 32.2% respectively on USG abdomen.[18 19] This is similar to the prevalence of NAFLD on USG abdomen reported by our study. Western Literature also reports prevalence of USG diagnosed NAFLD in general population to range between 17% to 46% depending upon the population studied.[20] The reported prevalence of NAFLD on USG abdomen from other countries like Italy[21](20%), Israel[22](30.5%), China[23](15.3% and 17.2%) and Srilanka[24](32%) is also similar to the prevalence reported by our study.

In an elegant study assessing the degree of hepatic steatosis using unenhanced CT of the abdomen and correlating the findings with Liver biopsy in prospective liver donors for living donor liver transplantation, Liver Attenuation Index (LAI) correctly predicted the degree of liver steatosis. LAI higher than +5 HU was associated with hepatic steatosis of 0-5% and LAI values ≤5 HU were associated with higher degree of hepatic steatosis (NAFLD). We used LAI of ≤5 HU to predict hepatic fat of more than 5% (NAFLD). Out of 124 prospective liver donors, 38(31%) donors on unenhanced CT of the abdomen had LAI of ≤ 5 HU and 86 donors (69%) donors had LAI of > 5 HU. Using LAI of ≤ 5HU to predict fatty liver, the prevalence of NAFLD in prospective liver donors using unenhanced CT was 31% in our study.

Magnetic Resonance Spectroscopy (MRS) directly measures the hepatic triglyceride content and has been found to be very useful for measuring hepatic fat content in prospective liver donors for living related liver transplantation. Out of 124 prospective liver donors included in our study, 61 (49%) donors had hepatic fat content of more than 5% on magnetic resonance spectroscopy while63(51%) donors had hepatic fat of less than 5%. Thus, the prevalence of NAFLD (Hepatic fat ≥ 5%) in our study on Magnetic Resonance Spectroscopy was 49%. Lee et al.[25] in his study reported NAFLD prevalence of 51%, that included 589 living donors and hepatic fat was measured using USG, CT, MRS and liver biopsy. MRS is known to have very high sensitivity, and specificity, in comparison to liver biopsy for measuring hepatic steatosis and has obviated the need for liver biopsy in certain situations.[26 30] Therefore Prevalence of NAFLD of 49% in our study is very similar to the prevalence of 51% reported by Lee et al. Marcos et al. from USA, using Liver biopsy to diagnose NAFLD found the prevalence of hepatic fat ≥30% to be 20% among prospective liver donors.[31]Petrowsky et al. reported variable degree of hepatic steatosis in 50% of patients planned for major liver resections which is similar to the prevalence in our study.[32]

In this study, liver biopsy was done in only 25 (20%) of 124 prospective liver donors. As has been discussed above, liver biopsy is dispensed with in many cases if imaging shows less than 5% fat on CT as well as MRS. As per our agreed protocol, liver biopsy was advised only to those prospective donors, who were predicted to have high liver fat (>20%) on basis of imaging or had unexplained transaminasemia on LFTs. Thus, most of the prospective liver donors who undergo liver biopsy at our institute are expected to have hepatic steatosis of ≥ 5% on histology. This is the reason that out of 25 prospective liver donors who underwent liver biopsy in our study 22 (88%) donors had hepatic fat of ≥5% and only 3 (12%) donors had hepatic fat of less than 5%. Hepatic steatosis diagnosed by histology is thus not representative of prevalence of NAFLD among the prospective donors in our study.

CONCLUSIONS AND RECOMMENDATIONS

The prevalence of Non Alcoholic Fatty Liver Disease (NAFLD) among apparently healthy prospective liver donors in this study was 23% on USG abdomen, 31% on unenhanced CT abdomen using LAI and 49% on Magnetic Resonance Spectroscopy (MRS). There is high prevalence of Non Alcoholic Fatty liver disease (NAFLD) among apparently healthy prospective liver donors. Hence screening of prospective liver donors for NAFLD is justified and is recommended.

REFERENCES

1. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of nonalcoholic fatty liver disease. Dig Dis2010; 28:155–161.
2. Christopher D. Byrne, Giovanni Targher. NAFLD: A multisystem disease. Journal of Hepatology 2015; 62: 47–S64.
3. Feng S. Increased donor risk: who should bear the burden? Liver Transpl2009; 15:570–573.
4. Durand F, Renz JF, Alkofer B, Burra P, Clavien PA, Porte RJ, et al. Report of the Paris consensus meeting on expanded criteria donors in liver transplantation. Liver Transpl 2008;14: 1694–1707.
5. Cameron A, Busuttil RW. AASLD/ILTS transplant course: is there an extended donor suitable for everyone? Liver Transpl 2005; 11:S2–5.
6. Loinaz C, Gonzalez EM. Marginal donors in liver transplantation. Hepatogastroenterology2000; 47:256–263.
7. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, Mullen KD, Cooper JN, Sheridan MJ. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002; 123: 745-750.
8. Kodama Y, Ng CS, Wu TT, Ayers GD, Curley SA, Abdalla EK et al. Comparison of CT methods for determining the fat content of the liver. AJR Am J Roentgenol 2007; 188:1307-12.
9. Rastogi R, Gupta S, Garg B, Vohra S, Wadhawan M, Rastogi H. Comparative accuracy of CT, dual-echo MRI and MR spectroscopy for preoperative liver fat quantification in living related liver donors. Indian J Radiol Imaging2016; 26:5-14.
10. Patrick Georgoff, David Thomasson, Adeline Louie, Estee Fleischman, Lauren Dutcher, Haresh Mani et al. Hydrogen-1 MR Spectroscopy for Measurement and Diagnosis of Hepatic Steatosis. AJR Am J Roentgenol 2012; 199(1): 2–7.
11. Kleiner DE, Brunt EM, Van Natta M et al. Design and validation of a histological scoring system for nonalcoholic steatohepatitis. Hepatology 2005; 41; 1313-1321. 11
12. McCormack L, Petrowsky H, Jochum W, Mullhaupt B, Weber M, Clavien PA. Use of severely steatotic grafts in liver transplantation: a matched case control study. Ann Surg 2007; 246:940–946.
13. Baccarani U, Isola M, Adani GL, Avellini C, Lorenzin D, Rossetto A, et al.Steatosis of the hepatic graft as a risk factor for post-transplant biliary complications. Clin Transplant2009.
14. Amarapurkar D, Kamani P, Patel N, Gupte P, Kumar P, Agal S, et al. Prevalence of non-alcoholic fatty liver disease: Population based study. Ann Hepatol 2007; 6: 161-3.
15. Anindo M, Puneet M, Sanjay S, Shashi K, Anand Kr, Chandrakant S Pandav. Prevalence of Nonalcoholic Fatty Liver Disease in an Adult Population in a Rural Community of Haryana, India.
16. Mohan V, Farooq S, Deepa M, Ravikumar R, Pitchumoni CS. Prevalence of non-alcoholic fatty liver disease in urban South Indians in relation to different grades of glucose intolerance and metabolic syndrome. Diabetes Res Clin Pract 2009; 84:84-91.
17. Das K, Das K, Mukherjee PS, Ghosh A, Ghosh S, Mridha AR, et al. Non obese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. Hepatology 2010; 51: 1593-602.
18. Singh SP, Nayak S, Swain M, Rout N, Mallik RN, Agrawal O, et al. Prevalence of non-alcoholic fatty liver disease in coastal eastern India: A preliminary ultrasonographic survey. Trop Gastroenterol 2004; 25:76-9.
19. Bajaj S, Nigam A, Luthra A, Pandey RM, Kondal D, Bhatt SP, et al. A case-control study on insulin resistance, metabolic co-variates & prediction score in non-alcoholic fatty liver disease. Indian J Med Res 2009; 129: 285-92.
20. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011; 34:274-285.
21. Bedogni G, Miglioli L, Masutti F, TiribelliC,Marchesini G, and Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. Hepatology 2005; 42: 44-52.
22. Zelber-Sagi S, Nitzan-Kaluski D, Halpern Z, and Oren R. Prevalence of primary non-alcoholic fatty liver disease in a population-based study and its association with biochemical and anthropometric measures. Liver Int2006; 26: 856-863.
23. Fan JG, Zhu J, Li XJ, Chen L, Li L, Dai F, Li F, and Chen SY. Prevalence of and risk factors for fatty liver in a general population of Shanghai, China. J Hepatol 2005; 43: 508-514.
24. Dassanayake AS, Kasturiratne A, Rajindrajith S, Kalubowila U, Chakrawarthi S, De Silva AP, et al. Prevalence and risk factors for non-alcoholic fatty liver disease among adults in an urban Sri Lankan population. J Gastroenterol Hepatol 2009; 24: 1284-8.
25. Lee JY, Kim KM, Lee SG, Yu E, Lim YS, Lee HC, Chung YH, Lee YS, Suh DJ. Prevalence and risk factors of non-alcoholic fatty liver disease in potential living liver donors in Korea: are views of 589 consecutive liver biopsies in a single center. J Hepatol 2007; 47: 239-244.
26. Wong VW, Chan RS, Wong GL, Cheung BH, Chu WC, Yeung DK, Chim AM, Lai JW, Li LS, Sea MM, Chan FK, Sung JJ, Woo J, Chan HL. Community-based lifestyle modification programme for non-alcoholic fatty liver disease: a randomized controlled trial. J Hepatol 2013; 59: 536-542
27. Ryan MC, Itsiopoulos C, Thodis T, Ward G, Trost N, Hofferberth S, O'Dea K, Desmond PV, Johnson NA, Wilson AM. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. J Hepatol 2013; 59: 138-143.
28. Noureddin M, Lam J, Peterson MR, Middleton M, Hamilton G, Le TA, Bettencourt R, Changchien C, Brenner DA, SirlinC, Loomba R. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in non alcoholic fatty liver disease trials. Hepatology 2013; 58: 1930-1940.
29. Le TA, Chen J, Changchien C, Peterson MR, Kono Y, PattonH, Cohen BL, Brenner D, Sirlin C, Loomba R. Effect of colesevelam on liver fat quantified by magnetic resonance in nonalcoholic steatohepatitis: a randomized controlled trial. Hepatology 2012; 56: 922-932.
30. Machann J, Thamer C, Stefan N, Schwenzer NF, KantartzisK, Häring HU, Claussen CD, Fritsche A, Schick F. Follow up whole-body assessment of adipose tissue compartments during a lifestyle intervention in a large cohort at increased risk for type 2 diabetes. Radiology 2010; 257: 353-363.
31. Marcos A, Fischer RA, Ham JM, Olzinski AT, Shiffman ML, SanyalAJ, Luketic VA, Sterling RK, Olbrisch ME, Posner MP. Transplantation 2000; 69: 2410-2415.
32. Petrowsky H, McCormack L, Trujillo M, Selzner M, Jochum W, Clavien PA.A prospective, randomized, controlled trial comparing intermittent portaltriad clamping versus ischemic preconditioning with continuous clamping for major liver resection. Ann Surg 2006; 244:921–928.