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World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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MINIREVIEWS

Opportunities for treatment of the hepatitis C virus-infected patient with chronic kidney disease

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Abstract

The prevalence of hepatitis C virus (HCV) infection amongst patients with chronic kidney disease (CKD) and end-stage renal disease exceeds that of the general population. In addition to predisposing to the development of cirrhosis and hepatocellular carcinoma, infection with HCV has been associated with extra-hepatic complications including CKD, proteinuria, glomerulonephritis, cryoglobulinemia, increased cardiovascular risk, insulin resistance, and lymphoma. With these associated morbidities, infection with HCV is not unexpectedly accompanied by an increase in mortality in the general population as well as in patients with kidney disease. Advances in the understanding of the HCV genome have resulted in the development of direct-acting antiviral agents that can achieve much higher sustained virologic response rates than previous interferon-based protocols. The direct acting antivirals have either primarily hepatic or renal metabolism and excretion pathways. This information is particularly relevant when considering treatment in patients with reduced kidney function. In this context, some of these agents are not recommended for use in patients with a glomerular filtration rate < 30 mL/min per 1.73 m^2. There are now Food and Drug Administration approved direct acting antiviral agents for the treatment of patients with kidney disease and reduced function. These agents have been demonstrated to be effective with sustained viral response rates comparable to the general population with good safety profiles. A disease that was only recently considered to be very challenging to treat in patients with kidney dysfunction is now curable with these medications.

Key words: Hepatitis C virus; Chronic kidney disease; Direct acting antiviral agents; Kidney transplantation

Core tip: Advances in the understanding of the molecular

biology of hepatitis C virus (HCV) have ushered in a new era in treatment. Recent studies have shifted the focus to the more difficult-to-treat cohorts of patients. The presence of chronic kidney disease and end stage renal disease were exclusion criteria for the pivotal clinical direct-acting antiviral agents trials, creating a group of patients with a large unmet medical need. This review will update the reader on the use of the direct acting antiviral agents in the HCV-infected patient with kidney disease. Recommendations for the timing of therapy, choice of agents and management of the kidney transplant candidate will be presented.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a recognized public health concern with global implications that affects approximately 170 million individuals worldwide[1-4]. Infection with HCV is associated with an increased morbidity and mortality secondary to hepatic injury and associated complications[4]. The infection, however, can also affect other organs with significant extrahepatic manifestations (Figure 1). Most noteworthy of these include insulin resistance, cryoglobulinemic vasculitis, sicca syndrome, neurocognitive dysfunction, B-cell non-Hodgkin lymphoma and an increase in cardiovascular adverse events[5-11]. On note, patients with HCV infection also have an increased incidence of proteinuria and chronic kidney disease (CKD)[5], often in the setting of essential mixed cryoglobulinemia or "idiopathic" membranoproliferative glomerulonephritis[5,9,12]. Furthermore, it has also been well established that patients with end stage renal disease (ESRD) have an even higher prevalence of HCV infection that is likely a consequence of greater blood product exposure and patient-to-patient transmission of disease within the dialysis clinics due to breakdowns in universal precautions[12,13].

This review will summarize the most recent data and treatment options recommended for HCV-infected patients with kidney disease. A population of patients that for years had extremely limited options for therapy can now be successfully and safely treated for eradication of HCV.

HCV AND THE KIDNEY

HCV-related glomerulonephritis with or without cryoglobulinemia

The HCV has an unusual tropism for B lymphocytes through linkage of envelope protein 2 and the CD81 molecule on the B cell. B cell activation can result in expansion of malignant cell lines or the production of unique antibodies that are of the IgM isotype and possess rheumatoid factor like activity[14-16]. As a consequence of these events, clinical syndromes including mixed cryoglobulinemia, lymphoproliferative disorders and glomerulonephritis with distinct histological patterns including membranous or membranoproliferative glomerulonephritis can be seen[5,6,17,18]. Of note, co-infected HIV/HCV patients have an increased mortality and an overall worse prognosis[19,20].

The glomerular diseases commonly associated with HCV infection are a consequence of the formation of circulating immune complexes that become trapped in the glomerular basement membrane. The clinical expression of this process can occur through type 2 mixed cryoglobulinemia with resulting type 1 membranoproliferative glomerulonephritis (GN), mesangial proliferative and focal proliferative GN, IgA nephropathy, membranous GN and polyarteritis nodosa[6,14,18]. Typically, the patient that develops cryoglobulinemia has been infected with HCV for many years. These patients may present with a skin rash (palpable purpura), polyneuropathy, multi-organ vasculitis, hypertension and the nephritic syndrome[14].

Suppression of viral replication is necessary to interrupt immune-complex production and subsequent injury to the kidney. The VASCUVALDIC study described the use of sofosbuvir and ribavirin in 24 patients with HCV-vasculitis syndrome and cryoglobulinemia. Patients were treated with direct-acting antiviral agents (DAAs) for 24 wk and achieved a sustained viral response at week 12 (SVR_{12}) of 74% with minimal side effects[21]. The less common presentation of an active vasculitic syndrome as part of the cryoglobulinemic syndrome requires a more aggressive treatment strategy targeted at the ongoing endothelial inflammatory process. Options include high dose corticosteroids, rituximab and therapeutic plasma exchange in addition to appropriate DAA therapy to eradicate viral replication[21-24].

Hepatitis C and CKD

HCV infection is highly prevalent in CKD patients[5] and HCV-infected patients have an increased risk for the development of CKD and proteinuria[5,25,26]. Furthermore, emerging data suggests that the rate of CKD progression to ESRD is greater when compared to non-infected patients[26-31]. In this context, HCV-infected patients with CKD stages Ⅰ (GFR > 90 mL/min per 1.73 m^2), Ⅱ (GFR 60-89 mL/min per 1.73 m^2) and Ⅲa (GFR 45-59 mL/min per 1.73 m^2) should be considered for DAA therapy with the goal to slow the progression of CKD. HCV-infected patients with CKD stages Ⅲb (GFR 30-44 mL/min per 1.73 m^2), Ⅳ (GFR 15-29 mL/min per 1.73 m^2) and Ⅴ (GFR < 15 mL/min per 1.73 m^2) will require a more individualized approach depending on the renal replacement therapy options being considered. The major decision point in this context is whether treatment should

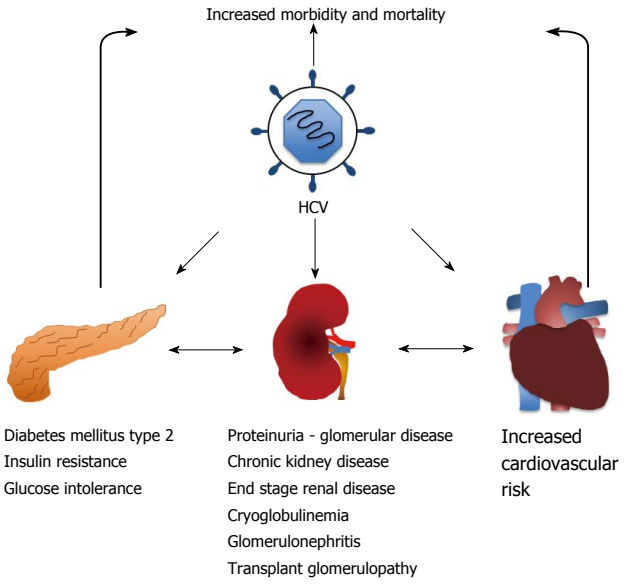

Figure 1 Extrahepatic manifestations of hepatitis C virus. HCV: Hepatitis C virus.

be recommended before or after kidney transplantation. Patients with a living kidney donor should be treated to achieve a SVR prior to transplantation. For the patient that is going to receive a deceased donor kidney the options may include delaying antiviral treatment in order to receive a kidney from an anti-HCV positive donor with the initiation of DAA treatment post transplantation. Alternatively, the patient could be treated pre-transplant and then transplanted with a kidney from an anti-HCV negative donor. Since not all centers currently accept kidneys from anti-HCV positive donors, this option is not available for all patients. Initial reports have demonstrated that accepting a kidney from a positive donor is associated with substantially shortened waiting time on the deceased donor waiting list in the United States[32-34]. Recent studies have demonstrated the safety and efficacy of DAAs in the kidney transplant recipient, with sustained viral response rates equal to that obtained in the general population with minimal side effects[35-37].

HCV in the ESRD patient

It is estimated that 5%-10% of the United States dialysis population is infected with HCV[38]. Many studies have demonstrated that HCV infection is associated with an increased risk of mortality and worse clinical outcomes in ESRD patients[39-43]. In a meta-analysis of ESRD patients, Fabrizi *et al*[41] found that HCV infection was associated with a relative risk of mortality of 1.35 (95%CI: 1.25-1.47). The increased morbidity and mortality associated with HCV infection emphasizes the systemic impact of this disease which can manifest with multiple extrahepatic manifestations and complications[5,40]. In this context, an increased cardiovascular risk attributable to HCV infection has been demonstrated in the ESRD patient[40]. In a recent update from the Dialysis Options and Practice Patterns Study data, it was concluded that HCV infection in ESRD patients was associated with an increased risk of death and hospitalization, anemia and worse quality of life scores for physical function, pain, vitality and mental health[44]. Relevant to any discussion on the associated risks accompanying HCV infection is whether successful treatment delivers a positive impact on outcomes. In this context, Hsu *et al*[45] reported that IFN-based therapy increased survival in HCV-infected ESRD patients. In another report, ESRD patients receiving IFN plus ribavirin obtained improved renal and cardiovascular outcomes compared to those who were untreated[46]. Prospective studies in ESRD patients will be necessary to determine if viral eradication alters the long-term outcome of this challenging population of patients with multiple co-morbidities.

HCV and kidney transplantation

Kidney transplantation is associated with an increase in long-term survival for ESRD patients with HCV infection[47,48]. This was clearly demonstrated in a longitudinal cohort study in which there was a decreased risk of death post-transplantation for the HCV-infected kidney transplant recipients when compared to those remaining on the waiting list[49]. This survival benefit was largely the result of a decrease in cardiovascular events within the first-year post-transplant[50].

HCV infection has been linked to several extra-hepatic manifestations that combine to increase morbidity and mortality after kidney transplantation[51]. It has been well established that HCV is the primary cause of liver disease in kidney allograft recipients[52] and these patients express an increased risk of insulin resistance and diabetes mellitus[53-58]. Furthermore, HCV-infected kidney recipients have a higher probability of developing transplant glomerulopathy[59] and recurrent membranoproliferative glomerulonephritis secondary to immune-complex injury to the renal allograft[60,61].

DIRECT ACTING ANTIVIRAL TREATMENT OPTIONS IN PATIENTS WITH CKD AND POST KIDNEY TRANSPLANT

The availability of DAAs with high SVR rates and favorable adverse event profiles allowed for the study of these drugs in patients with kidney disease, a group that had been excluded from of all the large pivotal trials. Emerging data are now demonstrating an excellent safety and efficacy profile in this patient population (Tables 1 and 2). The HCV-TARGET is a real-world study that collects data on the use of sofosbuvir-based regimens in HCV-infected patients. A total of 73 patients with a GFR $\leqslant$ 45 mL/min per 1.73 m^2 (n = 18 with GFR $\leqslant$ 30 mL/min per 1.73 m^2 and n = 5 on hemodialysis) were included in the analysis[62]. The SVR rate was 83% in patients with GFR $\leqslant$ 45 mL/min per 1.73 m^2 which was similar to patients with GFR > mL/min per 1.73 m^2, however patients with a GFR $\leqslant$ 45 mL/min per 1.73 m^2 had higher rates

Table 1 Direct acting antiviral agents: Dose and use in chronic kidney disease Ⅳ, Ⅴ, end stage renal disease and kidney transplant patients

Medication dose	Use in CKD stage Ⅳ, Ⅴ and ESRD	Use in kidney transplant patients - interactions with Immunosuppressant
Sofosbuvir/Simeprivir 400 mg daily/150 mg daily	CKD IV - GFR 15-29 mL/min: Not recommended CKD V - GFR < 15 mL/min: Not recommended ESRD (dialysis): Not recommended	Decrease in TAC levels with Simeprivir Increase levels of both CyA and Simeprivir Increase or decrease levels of SRL with Simeprivir No changes in TAC, CyA and SRL with Sofosbuvir
Sofosbuvir/Velpatasvir 400 mg/100 mg daily	CKD IV - GFR 15-29 mL/min: Not recommended CKD V - GFR < 15 mL/min: Not recommended ESRD (dialysis): Not recommended	Increase in TAC levels with Velpatasvir No changes in CyA levels with Velpatasvir Increase in SRL levels with Velpatasvir No changes in TAC, CyA and SRL with Sofosbuvir
Sofosbuvir/Daclastavir 400 mg daily/60 mg daily	CKD IV - GFR 15-29 mL/min: Not recommended CKD V - GFR < 15 mL/min: Not recommended ESRD (dialysis): Not recommended	No changes in TAC levels with Daclastavir No changes in CyA levels with Daclastavir Increase in SRL levels with Daclastavir No changes in TAC, CyA and SRL with Sofosbuvir
Sofosbuvir/Ledipasvir 400 mg/90 mg daily	CKD IV - GFR 15-29 mL/min: Not recommended CKD V - GFR < 15 mL/min: Not recommended ESRD (dialysis): Not recommended	No changes in TAC levels with Ledipasvir No changes in CyA levels with Ledipasvir No changes in SRL levels with Ledipasvir No changes in TAC, CyA and SRL with Sofosbuvir
Ombitasvir/Paritaprevir/ritonavir/Dasabuvir 12.5 mg/75 mg/50 mg × 2 tabs/250 mg × 2 tabs	CKD IV - GFR 15-29 mL/min: Dose adjustment not required CKD V - GFR < 15 mL/min: Dose adjustment not required ESRD (dialysis): Dose adjustment not required. Dialysis population studied. Minimal adverse events in patients with advanced CKD and ESRD on hemodialysis	Increase in TAC levels (ritonavir) Increase in CyA levels (ritonavir) Increase in SRL levels (ritonavir) No changes in TAC, CyA and SRL with Ombitasvir/Paritaprevir/Dasabuvir
Grazoprevir/Elbasvir 100 mg/50 mg daily	CKD IV - GFR 15-29 mL/min: Dose adjustment not required CKD V - GFR < 15 mL/min: Dose adjustment not required ESRD (dialysis): Dose adjustment not required. Dialysis population studied. Minimal adverse events in patients with advanced CKD and ESRD on hemodialysis	Increase in TAC levels with Grazoprevir Use of both CyA and Grazoprevir increase levels of Grazoprevir, contraindicated to use together Increase in SRL levels with Grazoprevir

GFR: Glomerular filtration rate; CKD: Chronic kidney disease; ESRD: End stage renal disease; TAC: Tacrolimus; CyA: Cyclosporine; SRL: Sirolimus.

of anemia, worsening kidney function and increased adverse events irrespective of the use of ribavirin[62]. Two open label treatment studies with simeprevir and dose-adjusted sofosbuvir exhibited high rates of SVR with a low incidence of adverse events in patients with advanced CKD and ESRD[63,64]. The RUBY-I trial evaluated the 3D regimen [ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (r) plus dasabuvir (DSV)] in patients with advanced CKD (stages 4/5) and on dialysis. SVR rates were 90% for patients with HCV genotype (GT) 1 with minimal side effects except for the patients with genotype 1a who received ribavirin as part of the protocol[65]. This group had more anemia events and required erythropoietin dose adjustments. Grazoprevir and elbasvir were studied in HCV-infected GT 1 patients with advanced CKD and ESRD in the C-SURFER trial. Sustained viral response rates of 99% were reported with a minimal adverse events profile[66]. The RUBY-I Cohort 2 study included patients with stage F4 fibrosis and GT 1a who were treated for 24 wk with the 3D regimen plus ribavirin. SVR_{24} rates of 89% were reported for this cohort with minimal side effects[67]. The RUBY-Ⅱ study evaluated the use of the 3D regimen in CKD 4 and 5 patients with HCV GT 1a (n = 13) infection without the addition of ribavirin. Genotype 4 patients received OBV/PTV/r without DSV (n = 5). Modified intention to treat (mITT) SVR_{12} rates of 100% were obtained in both groups[68]. Finally, a recent report described the use of glecaprevir (NS3/4A inhibitor) and pibrentasvir (NS5A inhibitor) in patients with advance kidney disease and HCV genotype 1-6 infection (n = 104). In this trial, patients with a GFR < 30 mL/min per 1.73 m^2 (n = 13 with GFR 15-29 mL/min per 1.73 m^2, n = 6 with stage 5 CKD and n = 85 on hemodialysis) obtained a 98% ITT SVR_{12} with no serious adverse events[69] and no viral relapses.

IFN-based protocols have not been recommended after kidney transplantation due to an unacceptably high incidence of rejection events. In contrast, DAA use in kidney transplant recipients has been shown to be safe and effective with minimal side effects[34-37]. Caution to avoid drug-drug interactions related to different drug metabolism/interactions (Table 1) is necessary in addition to high vigilance to maintain therapeutic calcineurin inhibitor levels as HCV viremia is suppressed[34,37].

The availability of DAA agents has dramatically changed the way HCV-infected patients with CKD and ESRD can be managed. While providing outstanding results, these excellent outcomes raise new questions as to which patients should be treated and when is the best time to initiate therapy. Further studies will be

Table 2 Direct acting antiviral agent options for patients with kidney disease

HCV/kidney disease consideration	Complications and observations from HCV infection	DAA options	Other DAA options/notes
HCV related acute glomerulonephritis with or without cryoglobulinemia	HCV has tropism for B-cells with subsequent: Mixed cryoglobulinemia Glomerulonephritis with distinct histological patterns: Membranous nephropathy Membranoproliferative GN	Sofosbuvir 400 mg/d combined with Simeprivir 150 mg/d Daclastavir 60 mg/d Velpatasvir 100 mg/d Ledipasvir 90 mg/d	Can use: Grazoprevir 100 mg/elbasvir 50 mg/d Ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg × 2 tabs/dasabuvir 250 mg × 2 tabs
The HCV-infected patient with stage 1-3a chronic kidney disease (GFR > 45 mL/min)	Increased risk for CKD development Increased rate of CKD progression to ESRD Higher mortality rate	Sofosbuvir 400 mg/d combined with Simeprivir 150 mg/d Daclastavir 60 mg/d Velpatasvir 100 mg/d Ledipasvir 90 mg/d	Can use Grazoprevir 100 mg/elbasvir 50 mg/d Ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg × 2 tabs/dasabuvir 250 mg × 2 tabs
The patient with advanced stage 3 and stage 4/5 chronic kidney disease (GFR < 45 mL/min)	Receiving an anti-HCV positive allograft decreases waiting times for a deceased donor kidney	Sofosbuvir 400 mg/d combined with Simeprivir 150 mg/d Daclastavir 60 mg/d Velpatasvir 100 mg/d Ledipasvir 90 mg/d	Sofosbuvir not recommended with GFR < 30 mL/min Can use Grazoprevir 100 mg/Elbasvir 50 mg/d Ombitasvir 12.5 mg/Paritaprevir 75 mg/ritonavir 50 mg × 2 tabs/dasabuvir 250 mg × 2 tabs
The ESRD patient on dialysis	Increased risk of mortality and poor clinical outcomes in ESRD patients Increased cardiovascular risk	Grazoprevir 100 mg/Elbasvir 50 mg/d Ombitasvir 12.5 mg/Paritaprevir 75 mg/ritonavir 50 mg × 2 tabs/dasabuvir 250 mg × 2 tabs	Grazoprevir/elbasvir, ombitasvir/paritaprevir/ritonavir/dasabuvir, Dialysis population studied Minimal adverse events in patients with advanced CKD and ESRD on hemodialysis
The kidney transplant recipient with eGFR > 30 mL/min	DAA use after kidney transplant is safe and well tolerated with SVR > 97%	Sofosbuvir 400 mg/d combined with Simeprivir 150 mg/d Daclastavir 60 mg/d Velpatasvir 100 mg/d Ledipasvir 90 mg/d	Can use Grazoprevir 100 mg/elbasvir 50 mg/d (caution with cyclosporin) Ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg × 2 tabs/dasabuvir 250 mg × 2 tabs

DAA: Direct-acting antiviral agent; GFR: Glomerular filtration rate; CKD: Chronic kidney disease; ESRD: End stage renal disease; HCV: Hepatitis C virus; DAA: Direct-acting antiviral; SVR: Sustained viral response.

necessary to answer these important questions.

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MINIREVIEWS

Imaging guided percutaneous interventions in hepatic dome lesions: Tips and tricks

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Abstract

Percutaneous hepatic interventions are generally safe given the fact that liver closely abuts the abdominal wall and hence it is easily accessible. However, the superior portion of liver, adjacent to the diaphragm, commonly referred as the "hepatic dome", presents unique challenges for interventionists. Percutaneous access to the hepatic dome may be restricted by anatomical factors and special considerations may be required to avoid injury to the surrounding organs. The purpose of this review article is to discuss certain specific maneuvers and techniques that can enhance the success and safety of interventions in the hepatic dome.

Key words: Hepatic dome; Radiofrequency ablation; Hepatocellular carcinoma; Percutaneous intervention

Core tip: Percutaneous interventions for lesions in the hepatic dome can be technically challenging. This review article discusses various maneuvers and techniques to safely access and treat lesions in this region.

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INTRODUCTION

Image guided hepatic interventions are integral to management of infective and neoplastic liver lesions[1-5]. A gamut of hepatic interventions including abscess drainage, thermal ablation, biopsy of focal liver lesions

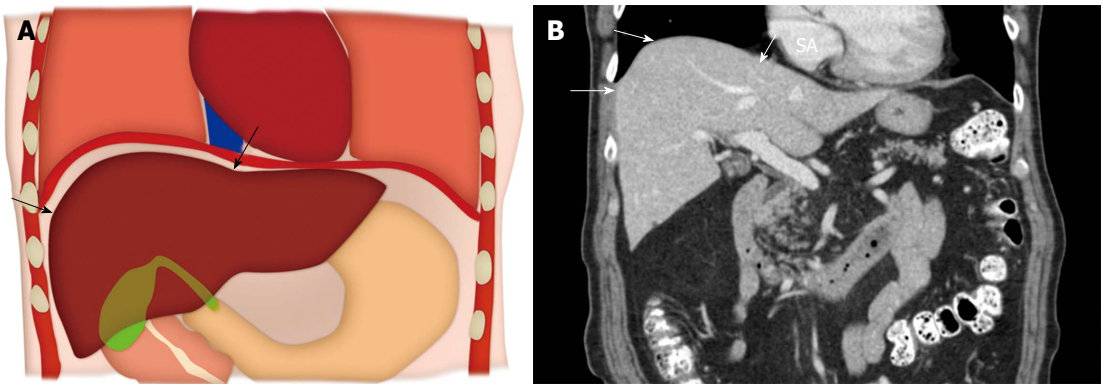

Figure 1 Anatomy of the hepatic dome. A: Colored schematic diagram; B: Coronal reformatted computed tomography image demonstrating the anatomy of the hepatic dome (arrows).

have significantly improved the morbidity and mortality associated with hepatic surgeries[1,2,4-6]. They offer several advantages over other invasive procedures in the liver such as laparascopy/laparotomy including absence of a laparotomy scar, shorter hospital stay, avoidance of general anesthesia and lower risk of complications, morbidity and mortality[2,4-6]. Liver lesions are generally easily accessible for percutaneous procedures, however access to certain regions may be challenging such as the hepatic dome. Certain interventional procedures in the hepatic dome, particularly thermal ablative procedures including radiofrequency ablation (RFA) can be associated with complications related to diaphragmatic and/or pleural injury[6]. Therefore, it is important to adhere to certain guiding principles of safety when performing percutaneous interventions in the hepatic dome. The purpose of this article is to review the anatomy, challenges, technical considerations and various different adjunctive maneuvers to safely access and treat lesions in the hepatic dome.

HEPATIC DOME: ANATOMIC CONSIDERATIONS AND TECHNICAL CHALLENGES

The term hepatic dome in general refers to the liver parenchyma close to the diaphragm and roughly accounts for nearly one-third of the liver volume. For most of its part, the hepatic dome is related on the anterior, lateral and posterior aspects to diaphragm, lung parenchyma with the accompanying pleura and thoracic cage (Figure 1). On the medial aspect, the hepatic dome is related to the cardia and inferior vena cava (IVC) anteriorly and the vertebral column posteriorly. Given the intricate anatomic relations, there is potential risk of severe pain during thermal ablative procedures due to diaphragmatic irritation that can limit complete treatment and can increase need for deeper sedation/anesthesia[7-12]. Percutaneous catheter drainage of hepatic dome abscesses can be difficult due to the need for transgression of the sterile pleural space and/or the lung which increases risk of pleural space contamination and the resulting pleural fluid collections and/or empyemas can often be challenging to treat[1].

Other technical challenge encountered during percutaneous intervention of hepatic dome lesions is accessibility and localization. The technical difficulty is particularly amplified in patients receiving conscious sedation or general anesthesia as the liver becomes increasingly subcostal in position due to shallow respirations brought on by sedation[13].

HEPATIC DOME INTERVENTIONS: TIPS AND TRICKS

Imaging modality

Ultrasound can be useful in approaching lesions of hepatic dome as various angles can be used, given non-axial nature of ultrasound imaging. However ultrasound guidance can be challenging for deeply seated lesions. Computed tomography (CT) provides a 3-dimensional orientation of the needle/catheter and the target during navigation and allows performance of several additional maneuvers as discussed later in the review article. CT permits fluoroscopic capabilities and allows access to the hepatic dome through the transpleural/transpulmonic route. Particularly in patients undergoing ablation, the role of CT encompasses planning, positioning of needles, ablation monitoring, verification of completion and post-ablation assessment. Disadvantages of CT include inability to visualize certain lesions thereby necessitating administration of intravenous contrast and exposure to ionizing radiation. C-arm cone beam CT (CBCT) application may be useful in hepatic dome interventions. Respiratory gating application in CBCT can minimize motion mis-registration during navigation in thoracic and hepatic dome tumors[14]. Ablations of the liver with CBCT are often performed after administration of intra-arterial or intravenous contrast and obtaining an intra-arterial access might

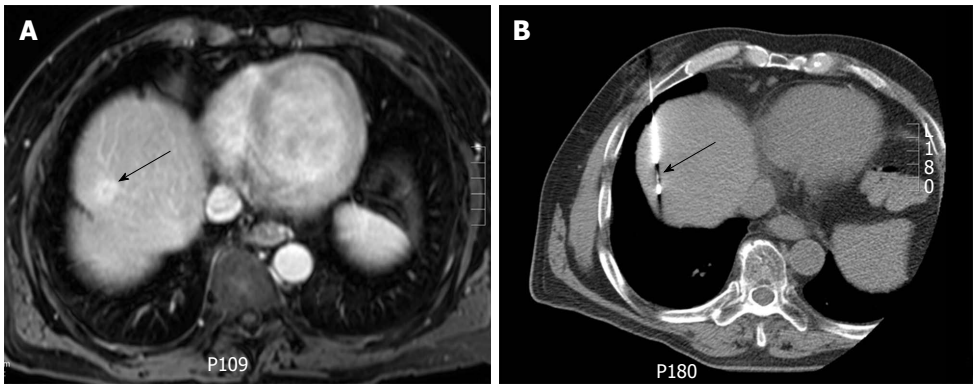

Figure 2 Computed tomography guided biopsy of a liver dome lesion in a 61-year-old man. A: Axial post gadolinium T1-weighted magnetic resonance image shows a 2 cm lesion (arrow) in the hepatic dome. On pre-procedural computed tomography, the tumor was not well seen and contrast could not be administered due to iodine allergy; B: Needle placement for biopsy was done based on use of anatomic landmarks (arrow) (configuration of inferior vena cava, cardiac margin and aorta) *via* a transpulmonary approach. Histopathology: Hepatocellular carcinoma.

be logistically difficult at certain centers[15,16]. Real time magnetic resonance imaging (MRI) guidance for biopsy of hepatic dome lesion has been described by Lu *et al*[3] to be beneficial in targeting lesions best depicted on MRI. MRI guidance has its own caveats such as need for specialized equipment (including open magnet configuration), limited availability and expertise.

Lesion localization

Precise lesion localization within the hepatic dome is crucial, particularly during biopsies and ablations to maximize diagnostic yield and achieve complete tumor destruction respectively. Accurate definition and localization of lesions on CT can be accomplished by either use of anatomic landmarks, contrast administration or additional techniques[17].

Extrapolation based on anatomic landmarks: Tumors seen on pre-procedural MR scans may not be well visualized on preliminary CT images or ultrasound during the procedure. In such circumstances, a comprehensive review of the imaging modality best depicting the lesion helps to identify the orientation of the lesion relative to adjacent landmarks such as blood vessels, bones, vascular or parenchymal calcification. Extrapolation of lesion relationship to hepatic veins, cardiac margin, aorta and IVC can be particularly helpful while performing interventions in hepatic dome. Sainani *et al*[17] reported that this strategy is highly accurate (98%) for percutaneous biopsy in liver and can obviate the need of intravenous contrast during the procedure (Figure 2).

Contrast administration: Administration of intravenous contrast can be used to guide exact placement of biopsy needle or RF electrode and is generally done after the guiding needle has been placed in to the presumed lesion location[11]. The relationship of the guiding needle and the lesion then facilitates the accurate placement of the biopsy needle or the RF electrode. It is important to ensure that the patient's serum urea and creatinine are within normal limits prior to administering contrast to avoid the risk of contrast induced nephropathy[18].

Other techniques: Several techniques have been described for targeting poorly visible hepatic lesions during interventional procedures[19-22]. Image fusion techniques combining real time ultrasonography with preprocedural CT/MRI images can be used effectively to enhance detectability for focal hepatic lesions with poor sonographic visibility[19,20]. A variety of tracking methods are available for image fusion such as image-based, optical, and electromagnetic tracking (most frequently used)[19]. The image fusion techniques however have limitations related to mis-registration because while the reference images (CT, MRI) are often obtained in a static breath-holding state, real-time ultrasound is affected by tissue deformation due to patient's respiration and movements. Most commercially available image fusion systems lack compensating mechanism for patient respiration and movement[23,24]. Hookwire and Suture localization under CT guidance followed by microwave ablation under ultrasound guidance for a sonographically invisible lesion has also been described by Kanazawa *et al*[21]. Such an approach however is cumbersome as it requires two different procedures for an ablation that can be entirely performed under CT guidance. Prior use of lipiodol might be helpful in the visualisation of hepatocellular carcinomas treated with lipoidal-transarterial chemoembolization (TACE)[22].

Optimizing access route

Selection of the approach and proper patient positioning are two important considerations for optimizing access to localization of lesions in the hepatic dome.

Percutaneous approach: The lesions of the hepatic dome can be accessed either by subcostal, intercostal or epipericardial fat pad approach. The choice of percutaneous approach is often based on operator

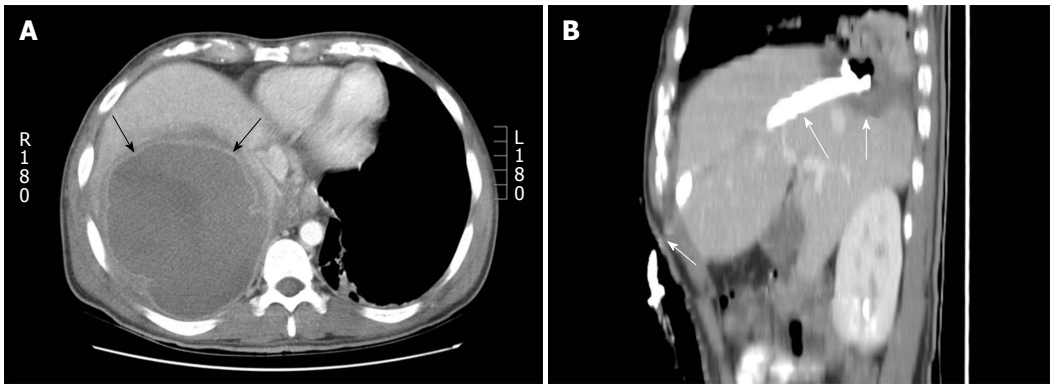

Figure 3 Percutaneous drainage of hepatic dome abscess in a 36-year-old man. A: Axial contrast computed tomography shows the large hepatic dome abscess (arrows). Pleural transgression carried an increased risk of pleural complications; B: Percutaneous catheter drainage using a subcostal approach (arrows) allowed successful abscess treatment while avoiding pleural transgression.

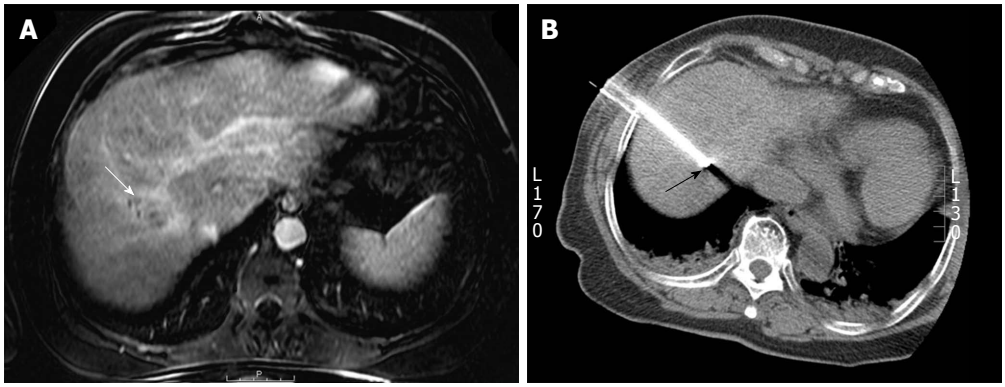

Figure 4 Percutaneous radiofrequency ablation of a hepatic dome hepatocellular carcinoma in a 54-year-old man. A: Axial post gadolinium T1-weighted image in the portal venous phase demonstrates a 3.4 cm hepatocellular carcinoma in the hepatic dome (arrow); B: During the radiofrequency ablation procedure, the patient was placed in the oblique position and using a lateral intercostal approach the tumor was accessed for a successful ablation (arrow).

experience and the access route to the regional anatomy of each individual patient is determined by reviewing prior imaging or preliminary scans. Subcostal approach is most preferred whenever feasible as this usually avoids transgression of lung and pleura (Figure 3). This approach is particularly beneficial in drainage of hepatic abscesses especially while using ultrasound guidance and can be facilitated by placing the patient in decubitus position. However this approach may not always be feasible and an intercostal route is frequently required (Figure 4) which may necessitate pleural or pulmonic transgression[1]. Pulmonary transgression can be avoided by creation of artificial pleural effusion or pneumothorax. Although pulmonary transgression may be unavoidable, for example, in patients with pleural adhesions[25]. In cases where pleural or pulmonary transgression is unavoidable it is important to limit the number of punctures to minimize the risk of pneumothorax. Furthermore, the interventionalist and patient must be prepared for the possibility of a pneumothorax and be aware of the management of such a complication. The technique of pulmonary transgression is of limited value in patients with severe emphysema or coagulopathy[25,26].

Brennan *et al*[27] described a novel epipericardial fat pad approach for safe access to hepatic dome lesions. The epipericardial fat pad is a variable sized structure located in the anterior mediastinum, outside the fibrous pericardium[27]. The authors recommend that an epipericardial fat pad exceeding 1 cm in thickness, may provide a safe window for percutaneous image guided RFA using CT fluoroscopy (Figure 5)[27].

Patient positioning: Optimal patient positioning not only determines a safe percutaneous path to the lesion but also ensures patient comfort and minimizes motion. An ideal position is one which allows the least complicated access to the hepatic dome. Supine position is the most common position employed and is generally the most comfortable one. It allows the use of anterior and lateral approach to access the dome (Figure 6). Oblique patient position can also be employed to improve the safety of a percutaneous path to the hepatic dome (Figure 4). Oblique patient position is usually employed when using a lateral approach to the hepatic dome. Lateral decubitus position can also be used when accessing the hepatic dome using a lateral approach. A lateral decubitus position is beneficial in

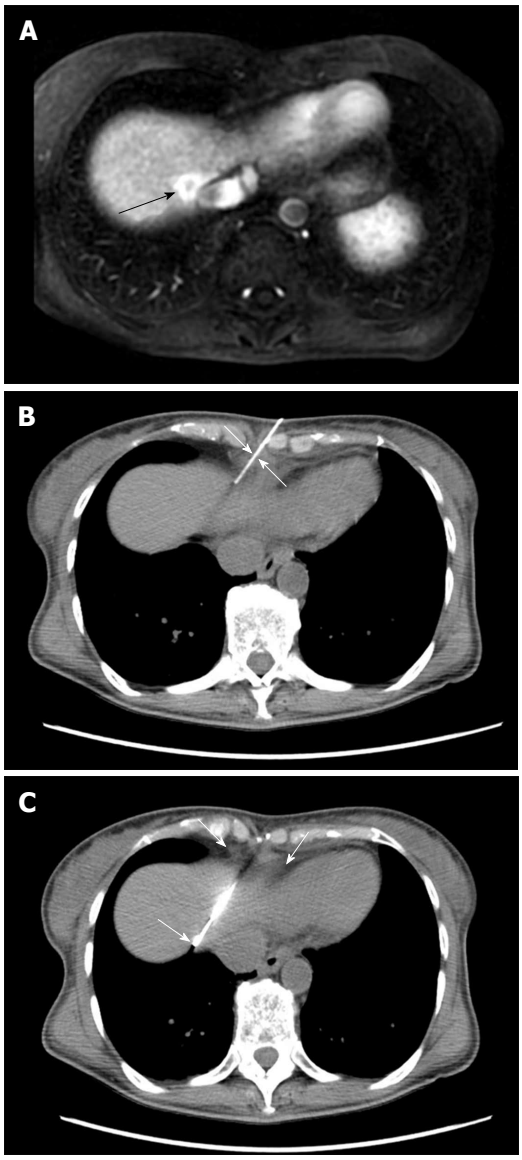

Figure 5 Computed tomography guided biopsy of a liver lesion adjacent to the inferior vena cava in a 56-year-old woman with breast cancer. A: Axial post gadolinium image T1 weighted magnetic resonance image demonstrates an enhancing lesion adjacent to the inferior vena cava (arrow); B and C: Intraprocedural computed tomography images demonstrate placement of the biopsy needle into the lesion through the epipericardial fat pad (arrows). Biopsy: Breast cancer metastases.

obese patients and women with large amount of breast tissue where an anterior approach is not feasible.

Adjunctive techniques

Non-target organ injury is the most feared complication during ablative procedures of hepatic dome. Several maneuvers could be performed in order to minimize collateral damage such as CT gantry angulation, creation of artificial ascites/pleural effusions and artificial pneumothorax.

Gantry angulation: Angulation of the CT gantry is a useful approach when the presence of overlying structures precludes a safe path to the hepatic dome (Figure 7). Angling the gantry allows optimum needle track visualization and permits a lower site of entry relative to lesion location, helping avoid transgression of pleura and lungs and thus reducing the risk of pneumothorax and pleural contamination. In this technique, the CT gantry is tilted towards the patient feet to achieve a caudo-cephalad beam direction. After preliminary scanning and identification of a safe path to the lesion, the needle shaft and hub are aligned to the CT gantry with the help of the localizing light. The needle is then advanced by constantly monitoring the needle tip position at frequent intervals while maintaining the angle of the needle. Gantry angulation technique is frequently performed for hepatic dome lesions and allows a subcostal approach to lesions high in the subphrenic location[28].

Hydro dissection/artificial ascites: Creation of artificial ascites or hydrodissection is an effective techniques for safe percutaneous ablation of hepatic dome lesions[7,8,29,30]. Hydrodissection involves injection of fluid into the peritoneal space around the liver to create separation of hepatic dome from the diaphragm, thereby preventing damage to the diaphragm and pleura during thermal ablation. Additionally, this technique diminishes post procedure pain resulting from diaphragmatic irritation, and reduces the need for general anesthesia for pain control allowing use of conscious sedation[30]. Hydrodissection can be performed using ultrasound or CT guidance and we most commonly use a 14-20 G Chiba needle or a 5 French vascular catheter/sheath for instilling fluid (Figure 8)[7,8,29]. For hepatic dome interventions, the puncture sites for creation of artificial ascites are typically at the level of left subphrenic space. Prolonged procedures such as ablations necessitate continued hydrodissection throughout the primary procedure to maintain sustained separation of the lesion from the diaphragm. Five percent dextrose water (D5W) is preferred over normal saline for hydrodissection since it provides significantly better electrical isolation, reduces unwanted heat dissipation to the adjacent organs and is least likely to cause volume shifts due to its iso-osmolar nature[7,8,29,31]. While no definitive amount of separation has been universally agreed upon, at least 5 mm separation between the diaphragmatic margin and liver capsule is recommended to minimize organ damage. The instilled fluid usually resorbs spontaneously within a week and does not decrease the therapeutic efficacy of RFA[29]. Despite its benefits, occasionally the fluid dissipates away from the intended site and hydrodissection is not effective in the presence of peritoneal adhesions due to prior treatments such as surgical resection, TACE or thermal ablation. Additionally, lesions located in the bare area of liver cannot be separated by hydrodissection as this area is surrounded by peritoneal ligaments. Omentum interposed during hepatic surgeries can also

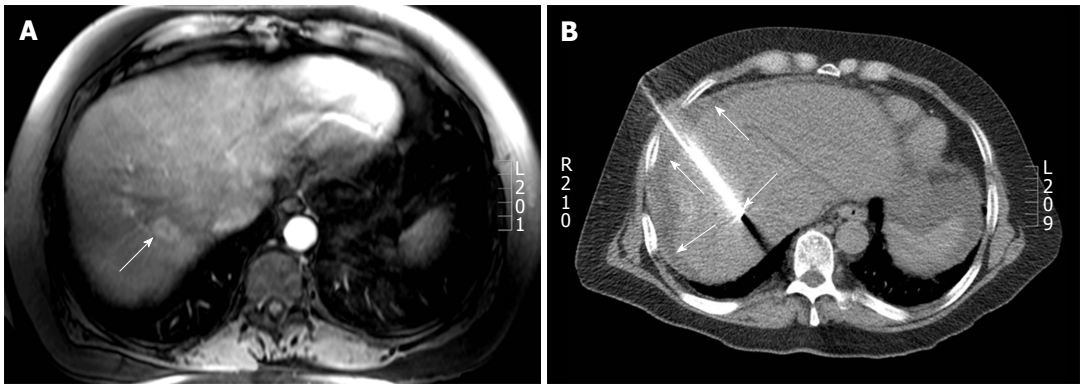

Figure 6 Computed tomography guided radiofrequency ablation in a 56-year-old lady with colorectal liver metastases. A: Axial post gadolinium T1 weighted magnetic resonance image shows a 2.7 cm (arrow) hepatic dome metastases; B: The radiofrequency ablation was performed with the patient in supine position and needle placement through the anterolateral intercostal approach. Hydrodissection was performed in this patient (arrows).

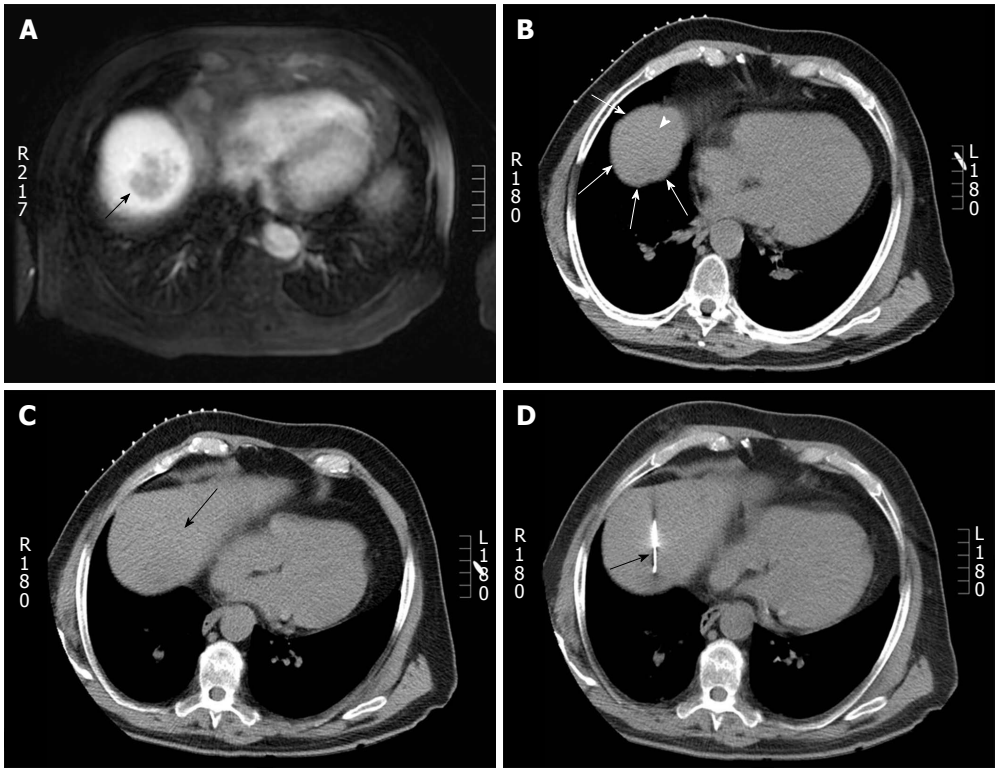

Figure 7 Computed tomography guided biopsy in a 65-year-old man. A: Axial post gadolinium magnetic resonance imaging shows a 4 cm hepatic dome lesion; B: On preprocedural CT, the lesion in the high dome is surrounded by lung (arrow head) on all sides. Pulmonic transgression was not possible as the patient had severe emphysema; C: The CT gantry was angulated in the craniocaudal direction (20 degrees) which created a safe path to the tumor from the anterior aspect (arrow); D: Axial intraprocedural CT image shows biopsy needle within the lesion (arrow). Biopsy: Hepatocellular carcinoma. CT: Computed tomography.

impede successful induction of artificial ascites[7].

Artificial pleural effusion: Bare area of liver (not lined by peritoneum) is in direct contact with the diaphragm. The fluid form an artificial ascites cannot dissect this region from the diaphragm. Similar situation arises when intra-peritoneal adhesions limit separation of the diaphragm from the liver. Artificial pleural effusion using saline is a valuable adjunctive technique in such situations. It also creates a safe percutaneous path or good sonographic window when using ultrasound for image guidance[32-36].

Iatrogenic pneumothorax: An iatrogenic pneumothorax can be created when other approaches fail[37,38]. In this technique, an 18 gauge epidural needle is appropriately positioned in the pleural space and around 50 mL of air, obtained through a micro-porous filter, is injected into the pleural space. Subsequently, serial boluses of 200, 400, 600 and 800 mL are injected to separate the lung from the pleura (Figure 9). Following completion of the interventional procedure, the intrapleural air is aspirated through the catheter into the syringe and expelled through the stopcock[37]. The patient is usually admitted overnight

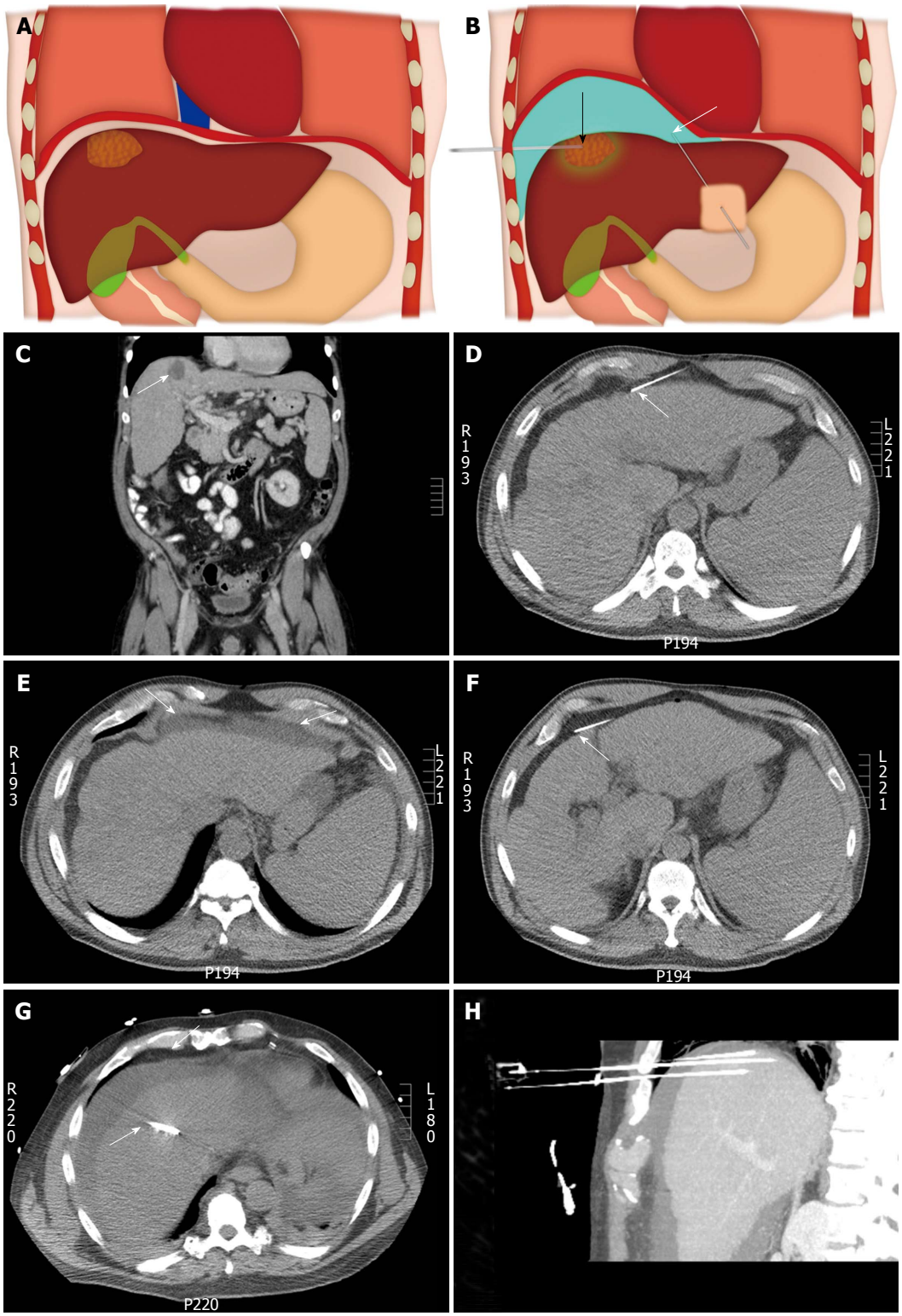

Figure 8 Illustration of the upper abdomen demonstrating the hydro-dissection technique. A: Coronal colored image shows a hepatic dome lesion very close to the diaphragm; B: Coronal colored image after hydro-dissection (shown in blue color) shows the separation of the dome of liver from the diaphragm which improves percutaneous access to the lesion and limits diaphragmatic injury. White arrow shows the needle for hydodissection and black arrow shows the needle into the lesion. An example of a hepatic dome lesion (C) (arrow) where hydrodissection was attempted by needle placed anteriorly (D) (arrow); E: Axial computed tomography showed accumulation of fluid within the properitoneal fat (arrows); F: The needle was repositioned with the tip of the needle into the peritoneal cavity (arrow); G: Successful hydrodissection achieved using instillation of 500 cc of D5W through the needle (arrow); H: The fluid was used to create a safe path for radiofrequency ablation of the hepatic dome hepatocellular carcinoma. Sagittal Maximum intensity projection image demonstrating the artificial ascites and electrodes in position in the hepatic dome lesion.

for observation and serial radiographs are obtained to monitor the resolution of the pneumothorax. Pneumothorax tends to accumulate in non-dependent locations and hence patient positioning is of critical

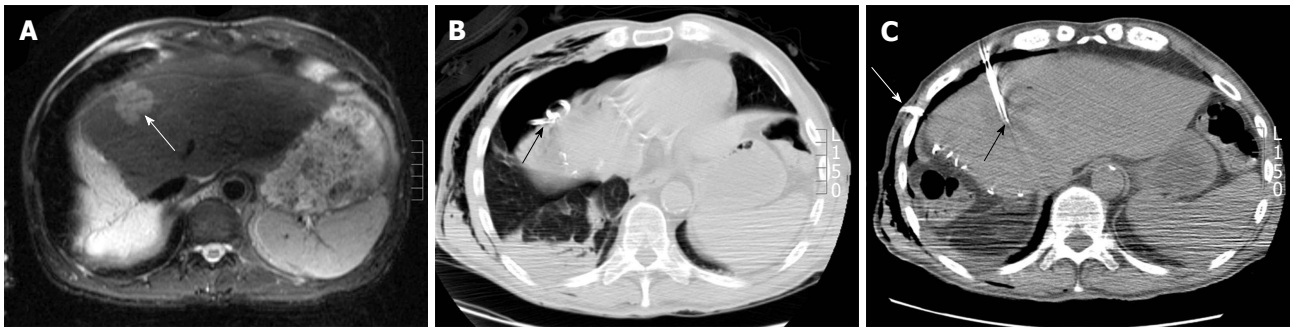

Figure 9 Artificial pneumothorax for radiofrequency ablation of hepatic dome hepatocellular carcinoma in a 69-year-old man. A: Axial T2WI magnetic resonance imaging shows A 4 cm lesion (arrow) in the hepatic dome; B: Artificial pneumothorax was created after instillation of intrapleural air. A chest tube was placed for drainage (arrow); C: Intra-procedural computed tomography shows radiofrequency electrode within the lesion for a successful ablation (black arrow).

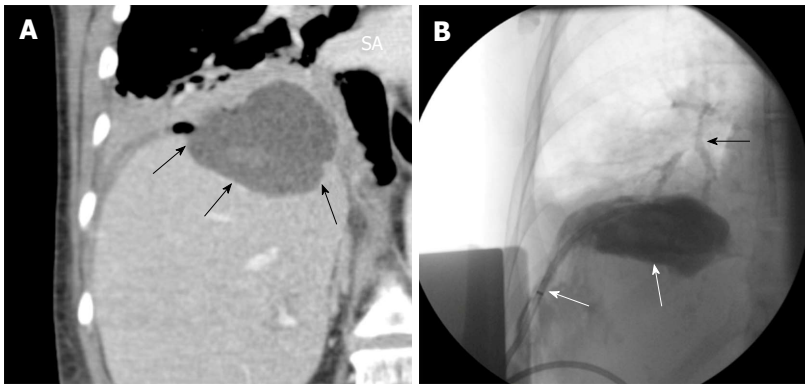

Figure 10 Hepatic abscess complicating a hepatic dome metastases ablation. A: Coronal reformatted image shows a abscess in the dome of liver (arrows); B: Percutaneous drainage was performed and drain injection shows communication with the bronchi (black arrow).

importance. For example, if anterior approach is adopted, the patient should be placed in supine position to direct the pneumothorax anteriorly[37].

Other techniques: Investigators have tried using different barriers for diaphragmatic protection such as intraabdominal carbon dioxide insufflations or angiographic balloon interposition, although the experience with their use is limited[10,39]. Raman *et al*[10] studied the use of intraperitoneal carbon dioxide insufflations for diaphragmatic protection during hepatic RFA ablations in porcine model and proved its efficacy in limiting diaphragmatic injury during superficial hepatic RFA. Knuttinen *et al*[39] interposed an angiographic balloon catheter during RFA ablation of the hepatic dome in a porcine model and demonstrated that balloon interposition is an effective technique for diaphragmatic protection. Balloon interposition has been reported to be superior to hydro-dissection or carbon dioxide insufflation, as the balloon remains stable during the procedure, while fluid and gas have a tendency to dissipate, however evidence in this regard is limited[39]. Electrode "retraction/torquing" technique is another maneuver with the use of expandable RFA probes in kidney, liver and lung tumors[40]. In this technique, the expandable electrode is retracted or torqued to displace the organ after the electrode is in position and fully expanded. This technique may be ineffective in isolation as only a few millimetres of displacement is achieved but could be used as an adjunct to other techniques.

COMPLICATIONS

Most dreaded complications during hepatic dome interventions include diaphragmatic and lung injury, pleural effusion, pneumothorax and empyema. Specific maneuvers like CT-guided transpulmonary needle insertion for liver tumors may lead to pneumothorax, lung hemorrhage and hemothorax, pleural effusion, diaphragmatic injury, tumor seeding in the pleura and/or lung parenchyma, lung abscess and systemic air embolism[26]. Serious complications such as massive pulmonary hemorrhage and systemic air embolism may result from transpulmonary RF needle insertion[41-43]. Diaphargmatic injury can lead to severe pain due to irritation, diaphragmatic palsy and/or perforation[7-10,30,31,39,44]. Diaphragmatic injury can also lead to fistulization of hepatic dome processes into the thorax (Figure 10). Injury to the lung and pleura can result in pneumothorax, pleural effusion and empyema which often need chest tube drainage[9,45]. The reported incidence of major diaphragmatic complications is low and has been reported to be more frequent with deployable radiofrequency electrodes and multiple treatments[29,46-49]. Post-ablation local

tumor progression may be slightly higher for peri-diaphragmatic tumors as compared to central tumors as these tumors are ablated more cautiously because of concern for collateral damage[50].

CONCLUSION

Image guided interventions in the hepatic dome often pose unique challenges to interventional radiologists. Interventionists should use their anatomic expertise along with the wide range of available imaging and interventional techniques to safely access and successfully manage hepatic dome lesions.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Improved Hepascore in hepatitis C predicts reversal in risk of adverse outcome

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Institutional review board statement: The study was reviewed and approved by the Sir Charles Gairdner Hospital Human Ethics Research Committee.

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Abstract

AIM

To establish if serial Hepascore tests (referred to as delta Hepascore) in those with chronic hepatitis C (CHC) correlate with the increase and/or decrease in risk of liver related complications.

METHODS

Three hundred and forty-six CHC patients who had two Hepascore tests performed were studied. During 1944 patient years follow-up 28 (8.1%) reached an endpoint. The Hepascore is a serum test that provides clinically useful data regarding the stage of liver fibrosis and

subsequent clinical outcomes in chronic liver disease.

RESULTS
Patients with a baseline Hepascore > 0.75 had a significantly increased rate of reaching a composite endpoint consisting of hepatocellular carcinoma, liver death, and/or decompensation (P < 0.001). In those with an initial Hepascore > 0.75, a subsequent improved Hepascore showed a significantly decreased risk for the composite endpoint (P = 0.004). There were no negative outcomes in those with a stable or improved delta Hepascore. The minimum time between tests that was found to give a statically significant result was in those greater than one year (P = 0.03).

CONCLUSION
In conclusion, Hepascore is an accurate predictor of liver related mortality and liver related morbidity in CHC patients. Of note, we have found that there is a decreased risk of mortality and morbidity in CHC patients when the patient has an improving delta Hepascore. Repeat Hepascore tests, when performed at a minimum one-year interval, may be of value in routine clinical practice to predict liver related clinical outcomes and to guide patient management.

Key words: Chronic; Prognosis; Direct acting antivirals; Serum; Hepatitis C

Core tip: The growing burden of hepatitis C is well recognized. The use of serum fibrosis markers such as Hepascore to monitor change in clinical risk in hepatitis C has a significant potential benefit to optimise the management in these patients. However, there is no information on the value of serial serum fibrosis tests and their improvement over time in determining changes in liver related clinical outcomes. We have found that there is a decreased risk of mortality and morbidity in chronic hepatitis C patients when the patient has an improving delta Hepascore, and serial tests may be of use in clinical practice.

Jeffrey AW, Huang Y, de Boer WB, Adams LA, MacQuillan G, Speers D, Joseph J, Jeffrey GP. Improved Hepascore in hepatitis C predicts reversal in risk of adverse outcome. *World J Hepatol* 2017; 9(19): 850-856 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i19/850.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i19.850

INTRODUCTION

The use of direct acting antivirals (DAA) therapy in chronic hepatitis C (CHC) treatment has resulted in up to 99% eradication of hepatitis C virus (HCV) in patients receiving treatment, depending on the genotype and type of DAA used[1,2]. The increased efficacy and minimal side effects of newer DAA's means that many more patients will access therapy, if financially able. To this end, in March 2016 the Pharmaceutical Benefits Scheme (PBS) in Australia listed sofosbuvir, ledipasvir/sofosbuvir and daclatasvir for the treatment with CHC (4) which will provide access to treatment for all Australians. It is estimated that there will be a 93% reduction in advanced liver disease cases due to the new DAA therapies compared to current regimens or no treatment[3]. HCV eradication has been shown to reduce liver fibrosis and liver related complications but the time required for this reversal is not known[2,4,5]. In addition, other co-factors such as NAFLD and alcohol use may be present and prevent or impair reversal of hepatic fibrosis. Therefore the problem remains that CHC patients with significant or advanced liver fibrosis at the time of successful HCV eradication may require long term monitoring for liver related complications for an uncertain period of time[6].

Fibrosis severity is currently measured non-invasively using serum fibrosis markers or transient elastography (Fibroscan®). The histopathological staging of fibrosis using liver biopsy has historically been the best predictor of liver related mortality and liver related morbidity associated with CHC[7]. However liver biopsy is now rarely used to stage CHC patients due to the risk of serious complications and issues with sampling error[8]. Several non-invasive serum fibrosis markers have been developed and are currently used as non-invasive alternatives to liver biopsy. Recent advances have now demonstrated that some serum fibrosis markers are able to directly predict adverse liver related outcomes rather than just provide a surrogate marker of liver fibrosis[9]. Hepascore is one of these markers, and it is used to predict liver related complications in patients with CHC. Hepascore has also been shown to be comparable to liver biopsy[10-12]. The Hepascore result itself ranges from 0 to 1.0 with a lower value indicating less severe or absent liver fibrosis and consequently better liver related clinical outcomes[10]. Measurement of the change in severity of liver fibrosis over time is also a strong prognostic tool in CHC[7]. The use of non-invasive serum fibrosis markers to monitor regression/progression of fibrosis in CHC has a significant potential benefit to optimise the clinical management in these patients. However, there is no information on the value of serial serum fibrosis tests and their change over time in determining changes in liver related clinical outcomes.

This aim of this study is to establish if serial Hepascore tests (referred to as delta Hepascore) in those with CHC correlate with the increase and/or decrease in risk of liver related complications.

MATERIALS AND METHODS

Cohort

Hepatitis C patients who presented to Sir Charles Gairdner Hospital (SCGH) based in Western Australia

from 1992 to 2012 and who also had two Hepascore tests performed were studied. We defined our inclusion criteria as all patients with hepatitis C, both treated and untreated. We also included patients regardless of if they achieved a sustained virological response (SVR). Our exclusion criteria consisted those with co-existing hepatitis B infection, human immunodeficiency virus as well as any other liver diseases. We also excluded patients who had received a previous liver transplantation. We received ethics approval for this study from the Department of Health Ethics Committee and the SCGH Ethics Committee.

Data collection

Baseline and second Hepascore test dates and results were collected for each patient. The WA based Data Linkage System, called WADLS was used to collect long term patient morbidity and mortality figures[13]. This is a wide scale population based linkage system that has been used extensively in the past and validated in previous population and cohort studies[14,15]. The WADLS contains records of cancer registrations as well as in-patient hospital morbidity and death records of the Western Australian population, from 1966 to the present. For this study, the events collected were all-cause mortality, liver related mortality, liver related morbidity and cancer registration. The WADLS database has previously been used as part of published and validated studies on liver fibrosis assessment and use of other non-invasive markers including Hepascore[10,11].

The primary endpoint for this study was liver related death (LRD) or liver transplantation. Secondary endpoints included onset of hepatocellular carcinoma (HCC) and liver decompensation (LD) of all causes. A composite endpoint included all of these endpoints but patients were only included once. The follow-up time used for the analysis of the baseline Hepascore test was from the time of the test until a primary or secondary endpoint or the conclusion of the study. The follow-up time used for the analysis of delta Hepascore was from the time of the second Hepascore test until an end point or end of study was reached. Delta Hepascore was calculated as the second Hepascore minus the baseline Hepascore. Patients who reached an endpoint before the second Hepascore test were excluded from delta Hepascore analysis. Hepascore is a serum marker that incorporates gamma glutamyl transpeptidase, hyaluronic acid and alpha 2 macroglobulin.

Statistical analysis

Statistics were undertaken using the SPSS Statistics software package and Kaplan-Meier survival analysis. Multivariate cox regression was used to assess the prognostic significance of an initial Hepascore, second Hepascore, and delta Hepascore to predict LRD, HCC or LD. Significance was defined as $P < 0.05$. Patients were placed into groups based on the baseline Hepascore value (0-0.25, 0.26-0.5, 0.51-0.75, 0.76-1.0) and the delta Hepascore (delta < -0.1, -0.1 $\leqslant$ delta $\leqslant$ 0.1, delta > 0.1) for the analysis. Survival probabilities for using baseline Hepascore values and delta Hepascore values were then calculated using Kaplan-Meier curves with significance calculated using the log rank test.

Area under Receiver Operating Characteristic (AUROC) curves were calculated to assess the capacity of baseline Hepascore and delta Hepascore values to predict liver related outcomes. The optimal time interval between Hepascore tests was assessed by Kaplan-Meier analysis according to the time between tests: < 1 year and $\geqslant$ 1 year.

RESULTS

A total of 346 patients met the inclusion criteria and were followed for a mean of 5.5 years, during which 28 (8.1%) had a LRD, developed LD and/or HCC (Table 1). The mean age of the cohort was 53.6 years and 220 (63.6%) were male. Of the total cohort, 8 (2.3%) had a LRD, 15 (4.6%) developed LD and 16 (4.3%) developed HCC. The mean baseline and second Hepascore values were 0.48 (SD ± 0.34) and 0.57 (SD ± 0.34) respectively and the mean delta Hepascore was 0.09 (SD ± 0.23). The time between Hepascore tests ranged from 0.03 and 12.5 years, with a mean of 3.3 and the mean follow-up time after the second Hepascore was 2.4 years. Multivariate cox regression showed that baseline Hepascore and delta Hepascore were independently predictive of reaching a composite clinical endpoint (LRD, HCC or LD), with *P* values of 0.02 and 0.013 respectively (Table 2).

Patients were grouped into 4 categories according to their baseline Hepascore (0-0.25, 0.26-0.5, 0.51-0.75 and 0.76-1.0). One hundred and twenty-nine (37%) had a Hepascore $\leqslant$ 0.25, 73 (21%) had a Hepascore from 0.26 to 0.5, 43 (12%) had a Hepascore from 0.51 to 0.75 and 100 (29%) had a Hepascore > 0.75. Kaplan-Meier survival curve analysis found that those patients with a baseline Hepascore > 0.75 had a significantly increased rate of LRD ($n \leqslant 0.001$), HCC ($n \leqslant 0.001$), LD ($n \leqslant 0.001$) and composite endpoint ($P < 0.001$) (Table 3 and Figure 1). Hazard ratios could not be calculated because of the lack of adverse liver related outcomes in the other three lower value Hepascore groups.

Patients with a baseline Hepascore > 0.75 were then analysed using the delta Hepascore value. The delta Hepascore values were divided into those with an improved Hepascore (delta < -0.1), a stable Hepascore (-0.1 $\leqslant$ delta $\leqslant$ 0.1) and a worsened Hepascore (delta > 0.1). Survival curve analysis found that in those with an improved Hepascore there was a significantly decreased risk of LRD, LD and a composite endpoint ($P = 0.048$, $P = 0.001$, $P = 0.004$ respectively) as shown in Figure 2. Twelve (17%) patients with a stable or worsened Hepascore reached a composite end point in contrast with those patients

Table 1 Patient characteristics and outcomes

Characteristic	All patients		Patients with first Hepascore > 0.75		All patients		Patients with first Hepascore > 0.75	
	Number	Percent	Number	Percent	mean	Range	mean	Range
Number	346	-	100	-	-	-	-	-
Gender (male)	220	63.6	76	76	-	-	-	-
SVR	38	11.0	16	16	-	-	-	-
Composite endpoint	28	8.1	21	21	-	-	-	-
LRD	8	2.3	8	8	-	-	-	-
LD	16	4.6	12	12	-	-	-	-
HCC	15	4.3	12	12	-	-	-	-
Result					-	-	-	-
Bilirubin (μmol/L)[1]	-	-	-	-	9.0	1.0-200	12	2.3-200
GGT (U/L)[1]	-	-	-	-	55.0	8.0-1005	93.5	17-713
HA (μg/L)[1]	-	-	-	-	30.3	1.0-1211	124.5	16-1211
A2M (μg/mL)[1]	-	-	-	-	2.5	0.6-6	3.6	1.5-6.0
Age (yr)	-	-	-	-	53.6	30-80	58.3	36-80
Baseline Hepascore	-	-	-	-	0.48	0.02-1.0	0.93	0.77-1.0
Second Hepascore	-	-	-	-	0.57	0.04-1.0	0.87	0.13-1.0
Delta Hepascore	-	-	-	-	0.09	-0.80-0.94	-0.06	-0.8-0.23
Time between baseline and second Hepascore (yr)	-	-	-	-	3.3	0.03-12.5	2.8	0.03-10.3
Follow-up after second Hepascore (yr)	-	-	-	-	2.2	0.01-7.3	1.9	0.01-5.7

[1]Serum markers used in Hepascore calculation. GGT: Gamma glutamyl transpeptidase; HA: Hyaluronic acid; A2M: Alpha 2 macroglobulin.

Table 2 Predictors of composite clinical endpoint (liver related death, hepatocellular carcinoma, liver decompensation) using Multivariate Cox Regression

Variable	Follow-up from the baseline Hepascore		Follow-up from the second Hepascore	
	P	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)
Baseline Hepascore	< 0.001	5.85 (2.25-15.18)	0.020	12.86 (1.49-111.17)
Second Hepascore	-	-	0.891	3288.82 (0.0-4.6E + 53)
Delta Hepascore	-	-	0.013	4.77 (1.35-16.45)

Table 3 Predictors of survival using Kaplan-Meier survival curves

Test	End point	*P* value (log rank)	Cohort size
Baseline Hepascore alone	Composite Endpoint	< 0.001	346
	LRD	< 0.001	352
	LD	< 0.001	348
	HCC	< 0.001	350
Delta Hepascore	Composite Endpoint	0.004	96
	LRD	0.048	105
	LD	0.001	101
	HCC	0.178	100

LRD: Liver related death; LD: Liver decompensation; HCC: Hepatocellular carcinoma.

Table 4 Predictors of survival Using Area under Receiver Operating Characteristic

Test	End point	AUROC
Baseline Hepascore alone	Composite endpoint	0.80
	LRD	0.89
	LD	0.75
	HCC	0.87
Baseline Hepascore > 0.75 and Delta Hepascore	Composite endpoint	0.84
	LRD	0.95
	LD	0.77
	HCC	0.93

AUROC: Area under Receiver Operating Characteristic; LRD: Liver related death; LD: Liver decompensation; HCC: Hepatocellular carcinoma.

who had an improved Hepascore, who had no negative outcomes. Comparison between those patients with a stable Hepascore and those with a worse Hepascore was not possible as 19.5% of patients had a baseline Hepascore value > 0.9 (the maximum Hepascore value is limited to 1.0). Thirty-eight (11%) patients had anti-viral treatment and reached a SVR. Of those achieving SVR only 4 patients reached an endpoint. Excluding these patients from the analysis made no difference to the results.

AUROC analysis was performed using the baseline Hepascore alone and with a combination of the baseline Hepascore and delta Hepascore (Table 4). There was a marked improvement in the AUROC for the combined baseline and delta Hepascore values compared to baseline Hepascore values alone with an AUROC for LRD of 0.95 and 0.89, for LD of 0.77 and 0.75 and for HCC of 0.93 and 0.87, respectively (Table 4).

Sub-group analysis was then completed to determine the minimum time required between Hepascore tests to determine delta Hepascore. Survival curve

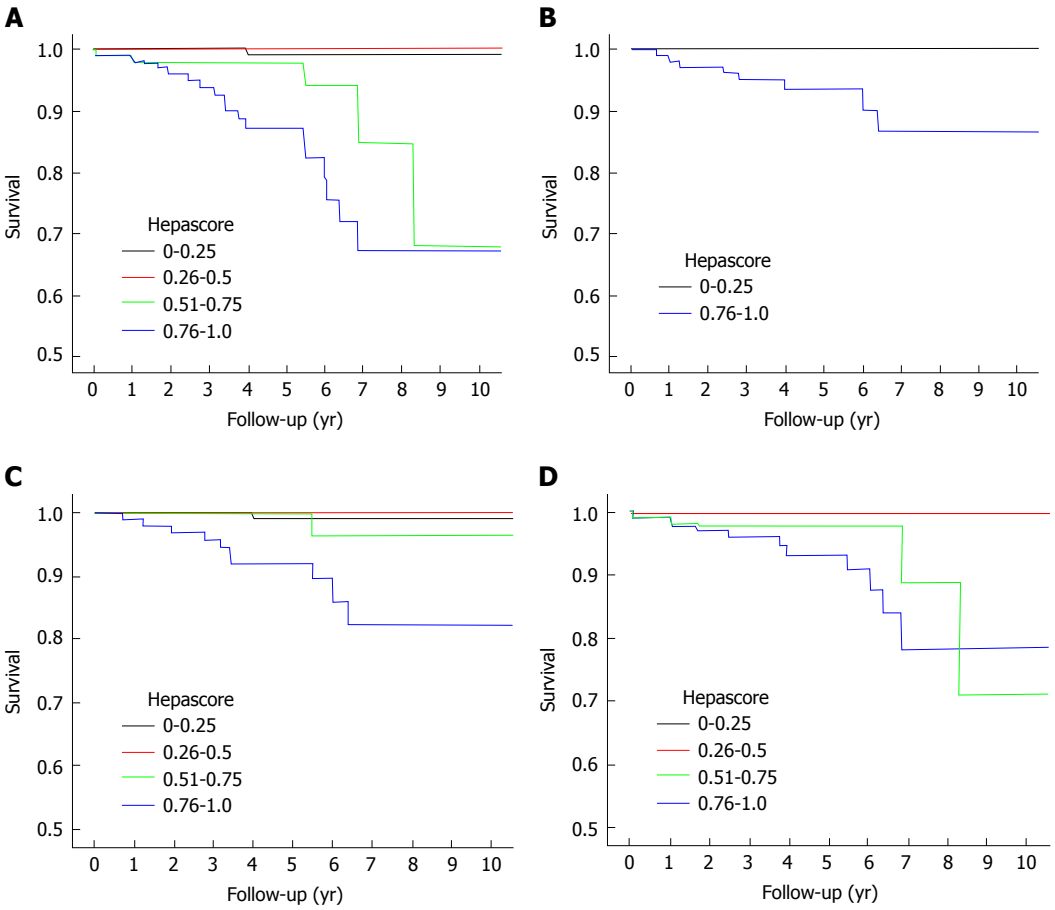

Figure 1 Kaplan-Meier curves specifying survival for liver related death, liver decompensation, hepatocellular carcinoma and a composite end point as a function of baseline Hepascore in the whole cohort. A: Time to composite end point using baseline Hepascore ($P < 0.001$); B: Time to LRD according to Hepascore ($P < 0.001$); C: Time to LD according to Hepascore ($P < 0.001$); D: Time to HCC according to Hepascore ($P < 0.001$). LRD: Liver related death; LD: Liver decompensation; HCC: Hepatocellular carcinoma.

analysis found that in those patients with a baseline Hepascore > 0.75, delta Hepascore is only predictive of a composite endpoint if the time between Hepascore tests is more than one year ($P = 0.03$) (Figure 3).

DISCUSSION

No previous studies have reported the use of repeated non-invasive serum fibrosis markers to predict improved liver related clinical outcomes. In this well documented cohort of CHC patients with a long follow-up period, 8.1% had an adverse liver related outcome after a mean of 5.5 years of follow-up. Cox regression found that a high (> 0.75) baseline Hepascore value was independently associated with increased rates of adverse liver related outcomes ($P < 0.001$), consistent with previous reports[11,12]. Importantly the delta Hepascore was also independently associated with predicting a composite clinical endpoint (LRD, HCC, LD) ($P = 0.004$). The AUROC for predicting the composite end point using the initial Hepascore and delta Hepascore was 0.84, which was increased compared to the AUROC using Hepascore alone (0.80).

Patients with an initial Hepascore value greater than 0.75 had an increased risk of developing an adverse liver related end point and this equated to a 5-year risk of 10% and a 10-year risk of 35%. CHC patients with an initial Hepascore less than or equal to 0.75 had a negligible (%) risk for developing these complications over 10 years. Further analysis found that in patients with a baseline Hepascore greater than 0.75 and who had a subsequent improvement in their second Hepascore of more than 0.1 (delta < -0.1), no adverse liver related end points occurred after a mean of 2.5 years. In contrast, those CHC patients with an initial Hepascore greater than 0.75 and who had a stable or worsened delta Hepascore there was an increased risk of experiencing an adverse liver related outcome. Hepascore has a range of values from 0 to 1.0, therefore only those patients with a baseline Hepascore below 0.9 could have an increased delta Hepascore (delta > 0.1) on subsequent testing. This limited the value of sub-group analysis comparing worsening (delta > 0.1) or stable ($-0.1 \leqslant$ delta $\leqslant 0.1$) delta Hepascore values in those with an initial Hepascore greater than 0.75.

The minimum time interval between Hepascore tests that resulted in useful clinical information was one year. Only when the Hepascore test interval was one year or more was there a significant association

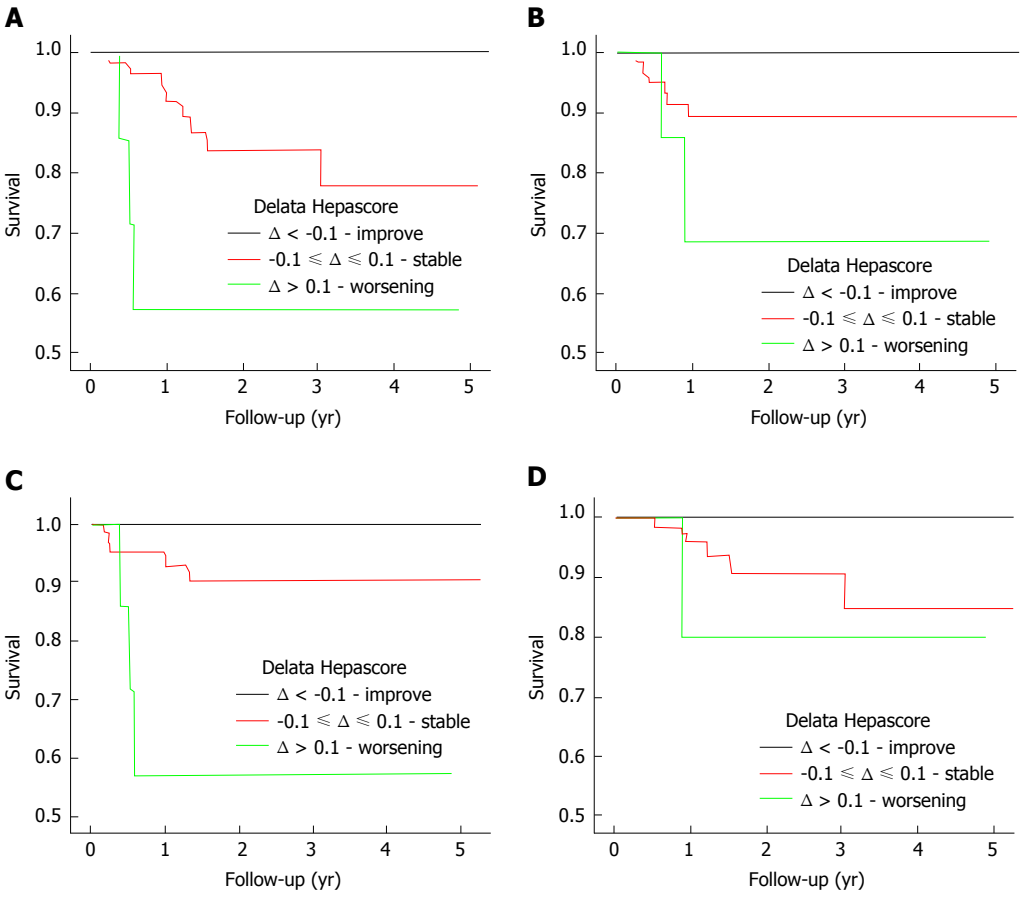

Figure 2 Kaplan-Meier curves specifying survival for liver related death, liver decompensation, hepatocellular carcinoma and a composite end point as a function of Delta Hepascore in the cohort with a baseline Hepascore > 0.75. A: Composite end point according to delta Hepascore, with a baseline Hepascore result of > 0.75 (P = 0.004); B: LRD according to delta Hepascore, with a baseline Hepascore result of > 0.75 (P = 0.048); C: LD according to delta Hepascore, with a baseline Hepascore result of > 0.75 (P = 0.001); D: HCC according to delta Hepascore, with a baseline Hepascore result of > 0.75 (P = 0.178). LRD: Liver related death; LD: Liver decompensation; HCC: Hepatocellular carcinoma.

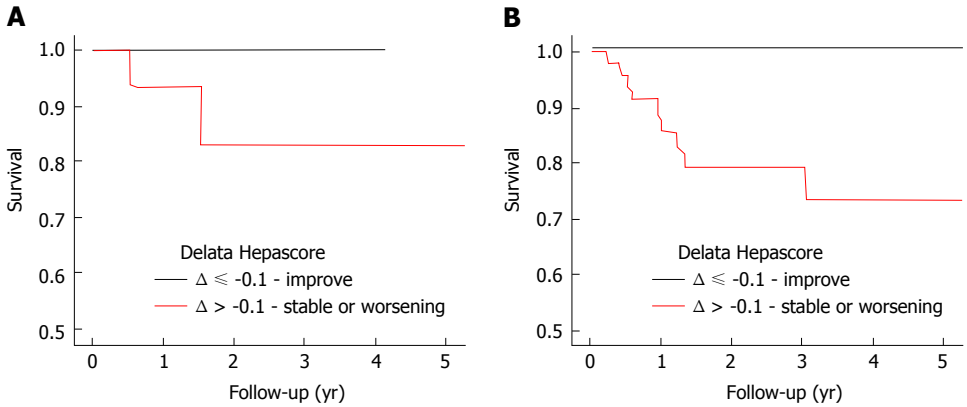

Figure 3 Kaplan-Meier curves specifying survival for a composite end point as a function of Delta Hepascore calculated at varying time intervals between tests. A: Time between tests - 0 to 12 mo (P = 0.347); B: Time between tests from - 1 year onwards (P = 0.03).

between delta Hepascore and the risk of adverse liver related outcomes (P = 0.03). Our findings show that there is a reduced risk of negative outcome in CHC patients who have an initial Hepascore over 0.75, but have an improved delta Hepascore, and will potentially allow a change in clinical management whereby the need for surveillance for varices and hepatocellular cancer may be reduced.

This study has some limitations. Firstly, due to the retrospective nature of this study, the second Hepascore test was not performed after a fixed time period. This time period was sufficient to demonstrate variation in delta Hepascore, however a fixed follow-up period could be established for future research.

Secondly, the data linkage system, which has allowed the collection of comprehensive data from a central source did not include information on alcohol consumption, diet and exercise. However, we believe that this data would not impact on the results of this study.

In conclusion, Hepascore is an accurate predictor of liver-related mortality and morbidity in CHC patients. Of note, we have found that there is a decreased risk of mortality and morbidity in CHC patients when the patient has an improving delta Hepascore. Repeat Hepascore tests, when performed at a minimum one-year interval, may be of value in routine clinical practice to predict liver related clinical outcomes and to guide patient management.

COMMENTS

Background

Several non-invasive serum fibrosis markers have been developed and are currently used as non-invasive alternatives to liver biopsy. Hepascore is one such marker that is able to predict severity of fibrosis, comparable to liver biopsy. Recent advances have now demonstrated that serum fibrosis markers such as Hepascore are able to directly predict adverse liver related outcomes rather than just provide a surrogate marker of liver fibrosis. Hepascore can also be used to monitor regression/progression of fibrosis in chronic hepatitis C (CHC).

Research frontiers

The use of Hepascore to monitor regression/progression of fibrosis in CHC has a significant potential benefit to optimise the clinical management in these patients. However, there is no information on the value of serial serum fibrosis tests and their change over time in determining changes in liver related clinical outcomes.

Innovations and breakthroughs

Hepascore was found to an accurate predictor of liver-related mortality and morbidity in CHC patients. Of note, the authors have found that there is a decreased risk of mortality and morbidity in CHC patients when the patient has an improving delta Hepascore. Repeat Hepascore tests, when performed at a minimum one-year interval, are of value in routine clinical practice to predict liver related clinical outcomes and to guide patient management.

Applications

Repeat Hepascore tests, when performed at a minimum one-year interval, may be of value in routine clinical practice to predict liver related clinical outcomes and to guide patient management.

Terminology

SVR: Sustained viral response. SVR is specific to hepatitis C and is the absence of HCV RNA for 24 wk after the cessation of treatment.

Peer-review

Current study was from the group who originally described Hepascore as a non-invasive marker of fibrosis in patients with chronic hepatitis C. In the current study, the authors use "baseline" Hepascore as a prognostic indicator. In addition, the authors also found the change in Hepascore over time ("Delta Hepascore") was also a predictor of liver related events or death.

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ORIGINAL ARTICLE

Prospective Study

Is hepatic steatosis associated with left ventricular mass index increase in the general population?

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Informed consent statement: All study participants provided informed consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Data sharing statement: Statistical code is available from the corresponding author. The data set can be requested from the Institute for Community Medicine, University Medicine Greifswald, 17489 Greifswald, Germany, under consideration of local data protection formalities.

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Abstract

AIM

To investigate the association between hepatic steatosis and change in left ventricular mass index (LVMI) over five years, and examine whether systolic and diastolic blood pressures are mediators of the association between hepatic steatosis and LVMI using a general population sample.

METHODS

We analyzed data from the Study of Health in Pomerania. The study population comprised 1298

individuals aged 45 to 81 years. Hepatic steatosis was defined as the presence of a hyperechogenic pattern of the liver together with elevated serum alanine transferase levels. Left ventricular mass was determined echocardiographically and indexed to height$^{2.7}$. Path analyses were conducted to differentiate direct and indirect paths from hepatic steatosis to LVMI encompassing systolic and diastolic blood pressure as potential mediating variables.

RESULTS

Hepatic steatosis was a significant predictor for all measured echocardiographic characteristics at baseline. Path analyses revealed that the association of hepatic steatosis with LVMI change after five years was negligibly small (β = -0.12, s.e. = 0.21, P = 0.55). Systolic blood pressure at baseline was inversely associated with LVMI change (β = -0.09, s.e. = 0.03, P < 0.01), while no association between diastolic blood pressure at baseline and LVMI change was evident (β = 0.03, s.e. = 0.05, P = 0.56). The effect of the indirect path from hepatic steatosis to LVMI *via* systolic baseline blood pressure was small (β = -0.20, s.e. = 0.10, P = 0.07). No indirect effect was observed for the path *via* diastolic baseline blood pressure (β = 0.03, s.e. = 0.06, P = 0.60). Similar associations were observed in the subgroup of individuals not receiving beta-blockers, calcium channel blockers, or drugs acting on the renin-angiotensin system.

CONCLUSION

Baseline associations between hepatic steatosis and LVMI do not extend to associations with LVMI change after five years. More studies are needed to study the longitudinal effects of hepatic steatosis on LVMI.

Key words: Hepatic steatosis; Left ventricular mass index; Blood pressure; General Population; Study of Health in Pomerania

Core tip: Data regarding the association between hepatic steatosis and left ventricular remodeling are limited and previous studies revealed conflicting results. In the present study, hepatic steatosis as defined by liver hyperechogenicity and increased alanine transferase levels was a significant predictor for all measured echocardiographic characteristics at baseline. In contrast, hepatic steatosis was not a predictor of relevance for left ventricular mass index (LVMI) change. Systolic and diastolic blood pressures did not mediate the association between hepatic steatosis and LVMI.

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INTRODUCTION

Hepatic steatosis is highly prevalent in Western countries and regarded as the hepatic manifestation of the metabolic syndrome[1]. Results from previous studies indicate that the metabolic syndrome and its components such as overweight and hypertension are associated with an increase in left ventricular mass (LVM)[2,3]. Data on the association between hepatic steatosis and LVM are limited; only four cross-sectional studies of small sample size exist addressing this relationship. The first study investigated the effect of hepatic steatosis on left ventricular geometry and function in normotensive, nondiabetic patients and demonstrated that patients with hepatic steatosis had mildly altered left ventricular geometry and early signs of left ventricular diastolic dysfunction compared to controls[1]. The second study analyzed the relationship between left ventricular morphology, metabolic parameters and hepatic steatosis in patients with hypertension and revealed that individuals with hepatic steatosis had a similar prevalence of left ventricular hypertrophy (LVH) compared to individuals without hepatic steatosis[4]. The third study using data from hypertensive, diabetic patients revealed that the frequency of LVH was higher in individuals with hepatic steatosis compared to individuals without hepatic steatosis. This study further showed that individuals with hepatic steatosis yielded 6-fold higher odds ratios for LVH than individuals without hepatic steatosis[5]. The fourth study was of case-control design and demonstrated that hepatic steatosis was significantly associated with left ventricular dysfunction in diabetic patients[6]. Due to the design of the aforementioned studies, inferences about effect directions between hepatic steatosis and left ventricular remodelling cannot be made. In particular, there is no differentiation between direct paths from hepatic steatosis to LVM progression or indirect effects *via* mediators. However, the evaluation of potential mediators is important for a better understanding of the mechanisms underlying a putative association between hepatic steatosis and LVM. We hypothesize that blood pressure is a potential key mediator on the path from hepatic steatosis to LVM as LVH is known to be the major cardiac sequel of hypertension[7,8]. Thus, blood pressure should be adequately considered in studies aimed to investigate the association between hepatic steatosis and LVM.

To our knowledge, there is no previous research providing data on the association between hepatic steatosis and left ventricular mass index (LVMI) encompassing the following criteria: (1) using a general population sample; (2) using longitudinal data to improve inferences on the direction of effects; and (3)

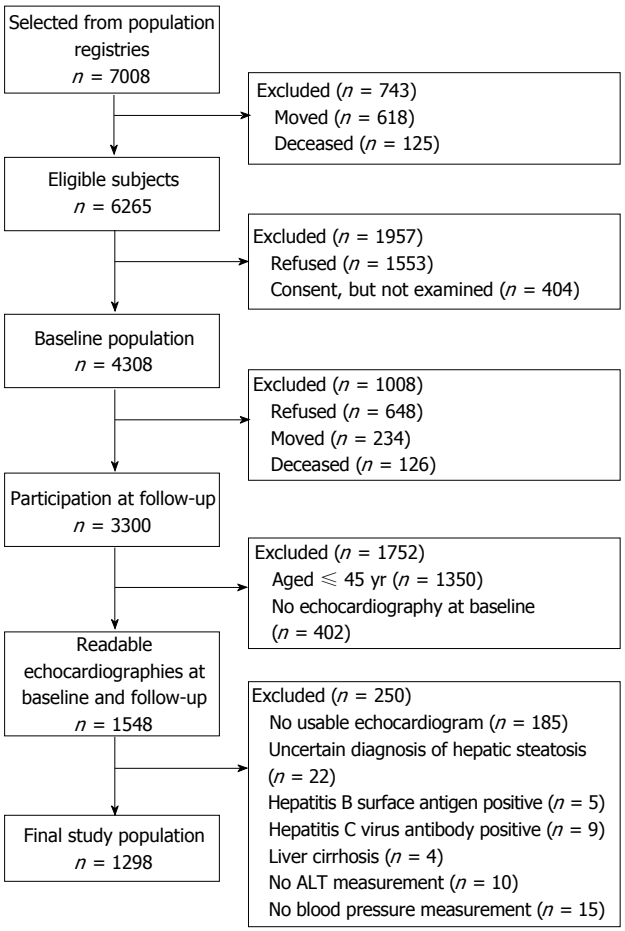

Figure 1 Flow-chart according to sample recruitment. ALT: Alanine transferase.

using methods to differentiate between direct and indirect pathways of hepatic steatosis on LVMI *via* blood pressure. The two major aims of the present study were, first, to investigate the association between hepatic steatosis and LVMI in a general population sample with prospective 5-year follow-up examination and, second, to analyze the mediating role of systolic and diastolic blood pressure on the pathway from hepatic steatosis to LVMI.

MATERIALS AND METHODS

Setting and study population

The Study of Health in Pomerania (SHIP) is a population-based cohort study conducted in West Pomerania, the northeastern area of Germany[9]. The sample recruitment procedure is displayed in Figure 1. At baseline, a sample of 7008 individuals aged 20 to 79 years was drawn from population registries. Only individuals with German citizenship and main residency in the study area were included. The net sample (without migrated or deceased persons) comprised 6265 eligible individuals. Each individual received a maximum of three postal invitation letters. In case of non-response, letters were followed by a phone call or by home visits. The SHIP population finally comprised 4308 participants (response 68.8%). Baseline examinations were conducted between 1997 and 2001. Between 2002 and 2006, all participants were re-invited for an examination follow-up, in which 3300 individuals (83.5% of eligible persons) took part[10]. Follow-up examinations were conducted on average 5.3 years after baseline (median: 5.0, 25th percentile: 5.0, 75th percentile: 5.3). All participants gave informed written consent. The study protocol was consistent with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the University of Greifswald. The study was monitored by a review board of independent scientists.

Among the 3300 participants with follow-up data, only those aged 45 years and older underwent echocardiographic examination at baseline (n = 1950). Of these, 1548 participants received a second echocardiography at follow-up. Readable echocardiograms from both examinations were available for 1538 individuals. Among these, 185 echocardiograms were not evaluable, 22 individuals had an uncertain diagnosis of hepatic steatosis, five were tested positive for hepatitis B surface antigen, nine were tested positive for anti-hepatitis C virus antibody, and four had a self-reported history of liver cirrhosis. Furthermore, ten participants had missing data on serum alanine transferase (ALT), and 15 participants lacked blood pressure measurements. Exclusion of these participants resulted in a final study population of 1298 individuals for the present analyses.

Measurements

Baseline assessments included data on demographics, behavioural risk factors, the individual's medical history and medication as well as data from somatometric, sonographic, echocardiographic and laboratory examinations.

Data on demographics, behavioral risk factors such as physical activity, alcohol consumption, and smoking status were collected using computer-assisted personal interviews. The following demographic variables were assessed: Gender, age and school educational attainment (in years of schooling completed). Individuals who participated in physical training during summer or winter for at least one hour a week were classified as being physically active. Alcohol consumption was assessed using a beverage-specific quantity-frequency measure: Number of days with alcohol consumption (beer, wine, spirits), and the quantity of alcohol consumed on such a day over the last month. Average daily consumption (in grams of pure ethanol) was calculated by multiplying frequency and amount, using beverage specific standard ethanol contents[11]. According to smoking habits, individuals were categorized into current, former, and never-smokers. Data on diabetes mellitus were obtained by self-reported physician's diagnosis of the disease.

The somatometric measures included body weight and height as well as waist circumference (WC). Height

and weight were measured for the calculation of the body mass index [BMI, weight (kg)/height^2 (m^2)]. WC was measured to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane, with the subject standing comfortably with weight distributed evenly on both feet.

Systolic and diastolic blood pressure were measured between 8 am and 7 pm three times after an initial five minute rest period at the right arm of seated individuals using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan). Each reading was followed by a further rest period of three minutes. One of two differently sized cuffs was applied according to the circumference of the participant's arm. The mean of the second and third measurement was calculated and used for the present analyses. Pulse pressure was defined as the difference between mean systolic and diastolic pressures. Hypertension was defined as systolic blood pressure $\geqslant$ 140 mmHg or diastolic blood pressure $\geqslant$ 90 mmHg or use of antihypertensive medication.

For the laboratory examinations, non-fasting blood samples were drawn from the cubital vein in the supine position. The laboratory takes part quarterly in the official national German external proficiency testing programs. In addition, internal quality controls were analyzed daily. Hepatitis B surface antigen and anti-hepatitis C virus antibodies were determined by enzyme-linked immunosorbent assays (AxSym HBSAG and AxSym HCV, Abbot, Abbot Park, IL, United States). Serum ALT levels were measured photometrically (Hitachi 704; Roche, Mannheim, Germany) and expressed as μmol/L × s, which corresponds to (μmol/L × s) × 60 = IU/L.

Sonographic examinations were performed by physicians using a 5 MHz transducer and a high resolution instrument (Vingmed VST Gateway, Santa Clara, CA, United States). The sonographers were unaware of the participants' clinical and laboratory characteristics. In SHIP, ultrasound examinations and readings underlie strict quality standards[12]. Hepatic steatosis was defined as the presence of a hyperechogenic liver pattern, with evident density differences between hepatic and renal parenchyma[13-15] together with increased serum ALT levels (> 75th percentile)[16].

Two-dimensional and M-mode echocardiography was performed by trained physicians using a Vingmed CFM 800A system (GE Medical Systems, Waukesha, WI, United States). All data and measurements were stored digitally. M-mode images of the left ventricle were recorded at the papillary level. Left ventricular dimensions [interventricular septum thickness (IVS), posterior wall thickness (LVPW), and left ventricular end-diastolic diameter (LVDD)] were measured off-line using the leading edge convention. LVMI was calculated as follows: LVMI = 0.80 × {1.04 × [(LVDD + IVS + LVPW)^3 − LVDD^3]} + 0.60/height$^{2.7}$[17,18]. LVH was defined as a LVMI of > 48 g/m$^{2.7}$ in men and > 44 g/m$^{2.7}$ in women[19]. Comparisons of intra-reader, intra-observer, inter-reader, and inter-observer LVMI measurements revealed Spearman coefficients of > 0.85 and differences in mean (± 2 SD) of < 5% (< 25%).

Statistical analysis

The study population was divided into two groups based on the presence or absence of liver hyperechogenicity and increased ALT levels at baseline: Category 1 comprised individuals without hyperechogenic liver pattern and without increased serum ALT levels and individuals fulfilling only one of the named criteria. Category 2 comprised individuals with hepatic steatosis as defined by both liver hyperechogenicity and increased serum ALT levels.

Using analyses of variance and χ^2-statistics, differences in baseline characteristics between individuals with and without hepatic steatosis regarding demographics, behavioural risk factors, and clinical characteristics were analyzed. Changes in echocardiographic parameters and blood pressure are depicted using absolute numbers and percentages. Bivariate correlations were calculated based on Pearson correlation coefficients.

We conducted path analyses to evaluate direct effects of hepatic steatosis on LVMI and the indirect effects *via* systolic and diastolic blood pressure. Standardized regression coefficients for systolic and diastolic blood pressure as well as LVMI are presented in the figures. The χ^2-value, comparative fit index (CFI), and the root mean square error (RMSEA) are provided as indicators of model fit. CFI is an incremental fit index comparing the fit of the model of interest with the independence model with values ranging from zero to one. RMSEA is a descriptive approximate estimation of the overall fit of the model in the population. Values have a lower bound of zero. A CFI > 0.96 and a RMSEA < 0.05 are commonly regarded as indicative of a satisfactory model fit[20,21]. Parameter estimates were obtained based on a robust weighted least square approach (WLSMV), which is suitable to handle categorical and non-normal data[21]. Age and sex were considered as independent predictors for all variables in the models. In addition, baseline body weight was included. LVMI was not regressed on body weight since body weight is part of the calculation of LVMI. The time of the day of blood pressure measurement was controlled for all indicators of blood pressure.

To evaluate possible bias due to missing data, we applied statistical inverse probability weights accounting for known individual characteristics of the study participants related to missing data on the echocardiographic examination at follow-up. These inverse probability weights were derived from logistic regression analyses with age, sex, body weight, waist circumference, alcohol intake, smoking, and a summative comorbidity index as predictors.

We repeated our analyses in the subgroup of indivi-

Table 1 General and echocardiographic characteristics of the study population with and without hepatic steatosis at baseline *n* (%)

	No/one criterion for hepatic steatosis *n* = 1106	US$^+$ and ALT$^+$ *n* = 192	*P*-value
Age (yr), M (SD)	59.6 (8.8)	57.2 (7.8)	$P < 0.01$
Male gender	442 (40.0)	139 (72.4)	$P < 0.001$
School education			n.s.
< 10 yr	570 (51.5)	102 (53.1)	
10 yr	358 (32.4)	67 (34.9)	
> 10 yr	178 (16.1)	23 (12.0)	
Waist circumference (cm), M (SD)	89.0 (11.5)	100.8 (10.9)	$P < 0.001$
Body weight (kg), M (SD)	75.6 (12.8)	88.6 (13.9)	$P < 0.001$
BMI, (kg/m^2), M (SD)	27.4 (4.3)	30.5 (4.6)	$P < 0.001$
Smoking			$P < 0.001$
Never-smoker	516 (46.6)	57 (29.7)	
Ex-smoker	382 (34.5)	99 (51.7)	
Current smoker	208 (18.8)	36 (18.8)	
Alcohol consumption (g/d), M (SD)	9.1 (14.5)	15.6 (19.5)	$P < 0.001$
Diabetes mellitus	100 (9.0)	26 (13.5)	$P < 0.001$
Systolic blood pressure (mmHg), M (SD)	139.3 (20.2)	148.5 (17.4)	$P < 0.001$
Diastolic blood pressure (mmHg), M (SD)	84.7 (10.8)	89.9 (10.4)	$P < 0.001$
Pulse pressure (mmHg), M (SD)	54.6 (14.7)	58.6 (13.4)	$P < 0.01$
Hypertension	660 (59.7)	163 (84.9)	$P < 0.001$
Intake of drugs with ATC07	239 (21.6)	39 (20.3)	n.s.
Intake of drugs with ATC08	140 (12.7)	28 (14.6)	n.s.
Intake of drugs with ATC09	198 (17.9)	58 (30.2)	$P < 0.001$
IVS, M (SD)	9.7 (2.2)	10.9 (2.5)	$P < 0.001$
LVEDD, M (SD)	50.9 (5.6)	52.4 (5.9)	$P < 0.01$
PWD, M (SD)	9.6 (1.9)	10.4 (2.0)	$P < 0.001$
LVM (g), M (SD)	181.8 (53.5)	215.8 (61.3)	$P < 0.001$
LVMI (g/m$^{2.7}$), M (SD)	46.2 (13.3)	51.0 (13.7)	$P < 0.001$
LVH	499 (45.1)	114 (59.4)	$P < 0.001$

Pearson χ^2 and ANOVAs were used for bivariate comparisons. Data are given as numbers and percentages or means (standard deviation). US: Ultrasound; ALT: Alanine aminotransferase; ATC: Anatomical-therapeutic code; IVS: Interventricular septum thickness; LVEDD: Left ventricular end-diastolic diameter; PWD: Posterior wall thickness; LVMI: Left ventricular mass index; LVH: Left ventricular hypertrophy; n.s.: Non-significant.

duals not receiving medication with possible influence on LVM [beta-blockers, anatomical-therapeutical (ATC) codes C07; calcium channel blockers, ATC codes C08; and drugs acting on the renin-angiotensin system, ATC codes C09] as sensitivity analysis.

P values were estimated for two-sided tests. A value of $P < 0.05$ was considered statistically significant. Statistical analyses were performed using STATA 10.2 (Stata Corporation, College Station, TX, United States) to conduct descriptive statistics. MPLUS 5.1 (Muthén and Muthén, Los Angeles, CA, United States) was used for path analyses. Data analyses were performed by Carsten O Schmidt who is an expert in the field of biomedical statistics.

RESULTS

Sample characteristics

At baseline, 1106 (85.1%) individuals fulfilled no or one criterion for hepatic steatosis, while 192 (14.9%) individuals had hepatic steatosis as defined by the combined presence of hyperechogenic liver pattern and increased serum ALT levels. LVH was present in 48.3% of the study population. The mean LVMI was 49.8 g/m$^{2.7}$ (SD = 14.7). General characteristics of the study population at baseline are presented in Table 1.

Baseline associations

Compared to individuals fulfilling no or one criterion for hepatic steatosis, individuals with hepatic steatosis were more often male, had lower educational attainment, a higher WC, a higher body weight, a higher BMI, were less often never-smokers and reported a higher average daily alcohol consumption. Moreover, individuals with hepatic steatosis reported more often diabetes mellitus, had higher systolic and diastolic blood pressure, higher pulse pressure and were more often hypertensive compared to individuals fulfilling no or one criterion for hepatic steatosis. Individuals with hepatic steatosis reported more often the intake of drugs acting on the renin-angiotensin system compared to the reference group. Regarding echocardiographic characteristics, individuals with hepatic steatosis showed a higher interventricular septum thickness, a higher posterior wall thickness, a higher left ventricular end-diastolic diameter, a higher left ventricular mass, a higher left ventricular mass index and more often left ventricular hypertrophy than the reference group.

Echocardiographic characteristics and blood pressure at baseline and follow-up

There was an increase in echocardiographic parameters from baseline to follow-up with higher values

Table 2 Echocardiographic characteristics and blood pressure at baseline and follow-up in the study population with and without hepatic steatosis

	Baseline M (SD)	Follow-up M (SD)	*P*-value
IVS, M (SD)			
No/one criterion for hepatic steatosis	9.7 (2.2)	11.2 (2.7)	$P < 0.001$
US$^+$ and ALT$^+$	10.9 (2.5)	12.0 (2.9)	$P < 0.001$
LVEDD, M (SD)			
No/one criterion for hepatic steatosis	50.9 (5.6)	48.8 (5.5)	$P < 0.001$
US$^+$ and ALT$^+$	52.4 (5.9)	50.6 (5.3)	$P < 0.001$
PWD, M (SD)			
No/one criterion for hepatic steatosis	9.6 (1.9)	9.9 (1.9)	$P < 0.001$
US$^+$ and ALT$^+$	10.4 (2.0)	10.9 (2.1)	$P < 0.01$
LVM (g), M (SD)			
No/one criterion for hepatic steatosis	181.8 (53.5)	192.2 (56.8)	$P < 0.001$
US$^+$ and ALT$^+$	215.8 (61.3)	226.1 (62.4)	$P < 0.01$
LVMI (g/m$^{2.7}$), M(SD)			
No/one criterion for hepatic steatosis	46.2 (13.3)	49.2 (14.6)	$P < 0.001$
US$^+$ and ALT$^+$	51.0 (13.7)	53.7 (14.4)	$P < 0.01$
SBP (mmHg), M (SD)			
No/one criterion for hepatic steatosis	139.3 (20.2)	136.3 (19.2)	$P < 0.001$
US$^+$ and ALT$^+$	148.5 (17.4)	142.8 (19.0)	$P < 0.001$
DBP (mmHg), M (SD)			
No/one criterion for hepatic steatosis	84.7 (10.8)	81.2 (10.3)	$P < 0.001$
US$^+$ and ALT$^+$	89.9 (10.4)	85.0 (11.1)	$P < 0.001$
LVH			
No/one criterion for hepatic steatosis	499 (45.1)	597 (54.0)	$P < 0.001$
US$^+$ and ALT$^+$	114 (59.4)	128 (66.7)	$P < 0.001$
Hypertension			
No/one criterion for hepatic steatosis	660 (59.7)	686 (62.0)	$P < 0.001$
US$^+$ and ALT$^+$	163 (84.9)	154 (80.2)	$P < 0.001$

IVS: Interventricular septum thickness; LVEDD: Left ventricular end diastolicdiameter; PWD: Posterior wall thickness; LVM: Left ventricular mass; LVMI: Left ventricular mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LVH: Left ventricular hypertrophy; US: Ultrasound; ALT: Alanine aminotransferase.

in individuals with hepatic steatosis compared to individuals fulfilling no or one criterion (Table 2). Blood pressure decreased from baseline to follow-up in both groups, while the proportion of hypertensive individuals slightly increased in the reference group and decreased in individuals with hepatic steatosis.

Cross-sectional correlations between hepatic steatosis, blood pressure and LVMI

Hepatic steatosis was significantly correlated with all variables in the path models, but effect sizes were small (standardized coefficients ranging from 0.11 to 0.17, Table 3). Baseline measures of LVMI and blood pressure were most closely related to their respective counterparts at follow-up. Systolic blood pressure was consistently more closely associated to LVMI than diastolic blood pressure.

Prediction of LVMI change

Figure 2 depicts the results of path analyses in the whole study population with systolic and diastolic blood pressure as potential mediators. The model fit was very good. Analyses revealed a very small, non-significant direct effect of baseline hepatic steatosis on LVMI change (β = -0.12, s.e. = 0.21, P = 0.55) and a negligible indirect effect *via* diastolic blood pressure (β = 0.03, s.e. = 0.06, P = 0.60, respectively). The moderate indirect effect *via* systolic blood pressure was borderline significant (β = -0.20, s.e. = 0.10, P = 0.07). Systolic blood pressure at baseline was inversely associated with LVMI change (β = -0.09, s.e. = 0.03, $P < 0.01$), while no association between diastolic blood pressure at baseline and LVMI change was evident (β = 0.03, s.e. = 0.05, P = 0.56).

Repeating our analyses after excluding individuals not receiving beta-blockers, calcium channel blockers or drugs acting on the renin-angiotensin system revealed similar results (Figure 3).

We further repeated our analyses after excluding 30 individuals with high risk drinking according to the recommendations of the World Health Organization (consumption levels of 40 g/d in women and > 60 g/d in men). Analyses revealed almost identical results (direct effect of baseline hepatic steatosis on LVMI change: β = -0.13, s.e. = 0.21, P = 0.54).

DISCUSSION

To the best of our knowledge, the present study is the first to investigate the association between hepatic steatosis and change in LVMI and the mediating role of systolic and diastolic blood pressure in this association using data from a prospective population-based cohort. While we observed relevant baseline

Table 3 Bivariate Pearson correlations

	Sex	Age	FLD	$LVMI_{t0}$	$LVMI_{t1}$	SBP_{t0}	SBP_{t1}	DBP_{t0}
Sex								
Age	-0.04							
FLD	-0.23[b]	-0.10[b]						
$LVMI_{t0}$	-0.12[b]	0.30[b]	0.13[b]					
$LVMI_{t1}$	-0.08[b]	0.26[b]	0.11[b]	0.62[b]				
SBP_{t0}	-0.21[b]	0.24[b]	0.16[b]	0.36[b]	0.24[b]			
SBP_{t1}	-0.13[b]	0.18[b]	0.12[b]	0.22[b]	0.22[b]	0.49[b]		
DBP_{t0}	-0.20[b]	-0.14[b]	0.17[b]	0.19[b]	0.11[b]	0.71[b]	0.32[b]	
DBP_{t1}	-0.15[b]	-0.28[b]	0.13[b]	0.04	0.05	0.28[b]	0.65[b]	0.52[b]

[b]$P < 0.01$. FLD: Fatty liver disease; $LVMI_{t0}$: Left ventricular mass index at baseline; $LVMI_{t1}$: Left ventricular mass index at follow-up; SBP_{t0}: Systolic blood pressure at baseline; SBP_{t1}: Systolic blood pressure at follow-up; DBP_{t0}: Diastolic blood pressure at baseline; DBP_{t1}: Diastolic blood pressure at follow-up.

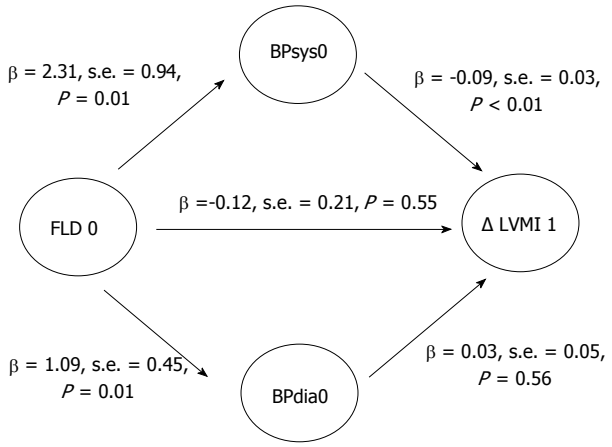

Figure 2 Path model for the effects of hepatic steatosis *via* systolic and diastolic blood pressure on left ventricular mass index in the whole study population (*n* = 1298). $\chi^2 = 3.2$, *df* = 3, *P* = 0.36; RMSEA < 0.01; CFI > 0.99. Indirect Effect *via* $BPsys_0$: β = -0.20; s.e. = 0.10; *P* = 0.07; Indirect Effect *via* $BPdia_0$: β = 0.03; s.e. = 0.06; *P* = 0.60. FLD: Fatty liver disease; LVMI: Left ventricular mass index; BPsys: Systolic blood pressure; BPdia: Diastolic blood pressure; RMSEA: Root mean square error; CFI: Comparative fit index; s.e.: Standard error.

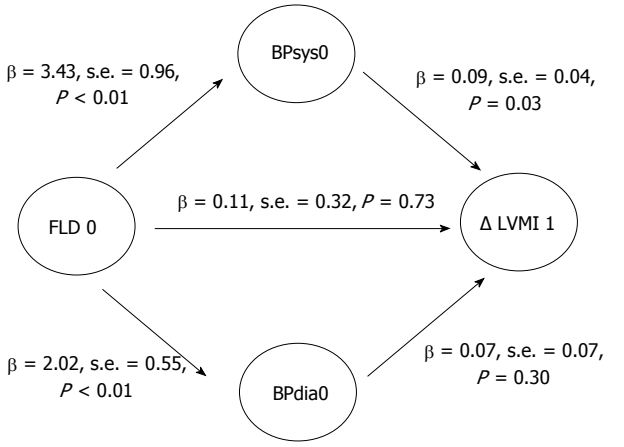

Figure 3 Path model for the effects of hepatic steatosis *via* systolic and diastolic blood pressure on left ventricular mass index in the subgroup of individuals without medication (*n* = 811). $\chi^2 = 1.9$, *df* = 3, *P* = 0.60; RMSEA < 0.01; CFI > 0.99. Indirect Effect *via* BPsys0: β = -0.30; s.e. = 0.17; *P* = 0.07; Indirect Effect *via* BPdia0: β = 0.15; s.e. = 0.14; *P* = 0.30. FLD: Fatty liver disease; LVMI: Left ventricular mass index; BPsys: Systolic blood pressure; BPdia: Diastolic blood pressure; RMSEA: Root mean square error; CFI: Comparative fit index; s.e.: Standard error.

associations between hepatic steatosis, blood pressure and LVMI, these associations were not relevant in the prediction of LVMI change. Our analyses suggest that hepatic steatosis is no predictor of relevance for LVMI change over time.

Previously, only four studies addressed the association between hepatic steatosis and left ventricular morphology[1,4-6]. These studies were of cross-sectional design, used data from small and inhomogeneous samples of patients and yielded conflicting results. The findings of the present study are in good agreement with results from the case-control study by Goland *et al*[1] demonstrating normotensive patients with hepatic steatosis to have larger intraventricular septum and posterior wall thickness and larger LVM than controls. In our study, LVM at baseline was 181.8 g in individuals fulfilling no or one criterion for hepatic steatosis and 215.8 g in individuals with hepatic steatosis. LVH was present in 45.1% of the individuals fulfilling no or only one criterion for hepatic steatosis and in 59.4% of the individuals with hepatic steatosis. Larger differences were found in the study by Mantovani *et al*[5] analyzing data from hypertensive, diabetic patients with hepatic steatosis. In that study, 82% of the patients with hepatic steatosis had LVH, while the proportion was 18% in patients without hepatic steatosis. Furthermore, patients with hepatic steatosis yielded 6-fold higher odds ratios for LVH compared to patients without hepatic steatosis. In contrast to the cross-sectional findings of our study, Bonapace *et al*[6] demonstrated no significant differences between patients with hepatic steatosis and patients without hepatic steatosis regarding left ventricular mass. Fallo *et al*[4] reported a comparable prevalence of LVH in patients with and without hepatic steatosis. However, that study was performed in hypertensive inpatients, in which a high prevalence of both FLD and LVH has been reported[4,22,23]. Therefore, the reported results cannot be directly compared with results from a general population sample.

Regarding longitudinal associations, we only found negligible direct effects of baseline hepatic steatosis

on LVMI change. We hypothesized that blood pressure is a mediating factor involved in the pathway from hepatic steatosis to LVMI as blood pressure has been found to be a major risk factor for left ventricular remodelling[24,25]. Yet, we failed to demonstrate indirect effects from hepatic steatosis on LVMI change *via* systolic and diastolic blood pressure. Interestingly, we observed an inverse association between systolic blood pressure at baseline and change in LVMI after five years. This finding is in contrast to previous studies revealing that both systolic and diastolic blood pressure are important correlates of LVM, whereas systolic blood pressure has been found to be more closely related to LVM than diastolic blood pressure[26]. Our data showed a drop in systolic and diastolic blood pressure from baseline to follow-up in the study sample, whereas this drop was more pronounced in individuals with hepatic steatosis than in individuals fulfilling no or one criterion for hepatic steatosis. We suppose that information on high blood pressure given by study physicians after baseline examination may have led to lifestyle modification or a rise in health consciousness in the study participants including the intake of blood pressure-lowering medication resulting in lower blood pressure at follow-up examination.

Regarding pharmacological interventions, treatment with antihypertensive drugs is indicated in the management of patients with cardiac hypertrophy, whereas the validity of data regarding the effects of antihypertensive medication on LVH regression is limited due to methodological weaknesses of existing studies[27]. Drugs acting on the renin-angiotensin system, beta blockers, and calcium channel blockers have been shown to diminish left ventricular mass with different efficacy[28]. In the present study population, 20.3% of the individuals with hepatic steatosis reported the intake of beta blockers, 14.6% the intake of calcium channel blockers and 20.3% the intake of drugs acting on the renin-angiotensin system. In addition to blood pressure lowering effects, these drugs may lead to LVMI regression[29]. It might be assumed that the observed decrease in blood pressure in the present sample was attended by LVMI regression covering a potentially present association between hepatic steatosis and LVMI. Repeating our analyses after excluding individuals taking beta blockers, calcium channel blockers, and drugs acting on the renin-angiotensin system confirmed our results in general. This finding indicates that the use of the respective medication did not have an influence on the association between hepatic steatosis and LVMI in the entire population as these drugs may prevent further increase of LVM or support regression of LVH[30,31].

Besides pharmacological treatment, lifestyle modification including weight loss and a reduction of alcohol and salt intake may contribute to LVH regression[29]. The role of physical activity remains controversial. It has been demonstrated that regular physical activity is associated with lower blood pressure and reduced cardiac remodeling, while exercise can also lead to the development of LVH[32]. In hypertensive individuals, exercise may have a positive effect on cardiac remodelling with regression or prevention of LVH[32].

With respect to alcohol consumption, analyses after excluding participants with high risk drinking did not change the results of our study. We therefore assume that alcohol consumption had no major role in the association between hepatic steatosis and LVMI. However, it needs to be considered that the number of individuals with high risk drinking was low and drinking above recommended levels is a risk factor for both hepatic steatosis and changes in cardiac structure.

In the present general population sample, both hepatic steatosis and LVH were highly prevalent stressing the public health relevance of these disease conditions in the general population.

Our study has several strengths, but also potential limitations that should be considered. Major strengths encompass the population-based longitudinal design, the large sample size and the high prevalence of hepatic steatosis and LVH in the study region[13,33]. Further strengths encompass the ultrasound and laboratory methods to detect hepatic steatosis and the strict quality management by standardized protocols and certified staff[9]. Limitations may arise from the inability to perform liver biopsy due to ethical concerns although known as the gold standard in the diagnosis of hepatic steatosis. Regarding methodological issues, path analyses allow for a useful differentiation of direct and indirect effects and therefore improve the interpretation of relationships among multiple variables. Limitations comprise potential selection bias due to selective drop out and initial non-response. However, previous analyses do not suggest a major effect on the outcomes under study[10,34]. More measurement points covering a larger time interval might be needed to improve our inferences on direct and indirect effects. Limitations may further arise from the inability to perform liver biopsy due to ethical concerns although known as the gold standard in the diagnosis of hepatic steatosis.

We conclude that hepatic steatosis as defined by liver hyperechogenity and increased ALT levels was not a predictor of relevance for LVMI change after five years in the present population-based cohort of individuals aged 45 to 81 years. Nevertheless, both hepatic steatosis and LVH were highly prevalent in the present indicating the importance of both disease conditions in the general population and the necessity for risk factor reduction to avoid subsequent morbidity and mortality.

COMMENTS

Background

Hepatic steatosis is highly prevalent in Western countries and regarded as the hepatic manifestation of the metabolic syndrome. The metabolic syndrome and its components such as overweight and hypertension are associated with

an increase in left ventricular mass (LVM). Data on the association between hepatic steatosis and LVM are limited; only four cross-sectional studies of small sample size exist addressing this relationship. Due to the design of the aforementioned studies, inferences about effect directions between hepatic steatosis and left ventricular remodelling cannot be made. In particular, there is no differentiation between direct paths from hepatic steatosis to LVM progression or indirect effects *via* mediators.

Research frontiers

There is no previous research providing data on the association between hepatic steatosis and left ventricular mass index (LVMI) encompassing the following criteria: (1) using a general population sample; (2) using longitudinal data to improve inferences on the direction of effects; and (3) using methods to differentiate between direct and indirect pathways of hepatic steatosis on LVMI *via* blood pressure.

Innovations and breakthroughs

The present study is the first to investigate the association between hepatic steatosis and change in LVMI and the mediating role of systolic and diastolic blood pressure in this association using data from a prospective population-based cohort.

Applications

The authors conclude that hepatic steatosis as defined by liver hyperechogenity and increased ALT levels was not a predictor of relevance for LVMI change after five years in the present population-based cohort of individuals aged 45 to 81 years. Nevertheless, both hepatic steatosis and LVH were highly prevalent in the present study population indicating the importance of both disease conditions in the general population and the necessity for risk factor reduction to avoid subsequent morbidity and mortality.

Peer-review

This is an interesting and well-written manuscript. This study investigated the association between hepatic steatosis and change in LVMI over 5 years in a study population of 1298 individuals aged 45 to 81 years. Hepatic steatosis was demonstrated to be a significant predictor for all measured echocardiographic characteristics at baseline but not for LVMI change.

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