

Review

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Review

Metabolic Dysfunction-Associated Steatotic Liver Disease and Pancreaticoduodenectomy; A Narrative Review

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Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become increasingly recognized as a postoperative complication in patients undergoing pancreatic surgeries, particularly pancreaticoduodenectomy (PD). Given MASLD's prevalence and impact on liver function and postoperative outcomes, understanding its incidence, risk factors, and potential interventions is critical for patient care. This study reviewed the relation between MASLD and PD. Studies indicate that MASLD's incidence ranges from 13.2% to 31% in post-PD patients, with notable variation influenced by factors such as sex, body mass index, and nutritional deficiencies. PD, performed to treat pancreatic or bile duct disease, is associated with considerable postoperative physiological changes. These include disruptions in pancreatic enzyme production, which can impair digestion, metabolism, and potentially contribute to MASLD in susceptible patients. Patients with MASLD post-PD show lower liver-to-spleen attenuation ratios on imaging and often require intensified pancreatic enzyme replacement. A scoring system based on risk factors has been developed to identify patients at higher risk of MASLD and guide preventive nutritional support. MASLD is a prevalent complication post-PD that impacts recovery and treatment continuity in cancer patients. Early risk stratification, tailored enzyme therapy, and ongoing monitoring may reduce MASLD-related liver impairment, enhancing patient outcomes.

Keywords: NAFLD; pancreas; bile duct; hepatic steatosis; outcome

Background

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), has emerged as a significant global health concern, affecting approximately 25-40% of the world's population [1,2]. This chronic liver condition is closely associated with metabolic syndrome, obesity, and type 2 diabetes mellitus [3]. As the prevalence of MASLD continues to rise, its impact on various aspects of patient care, including surgical outcomes, has become increasingly apparent [2,4,5].

Pancreaticoduodenectomy (PD), also known as the Whipple procedure, is a complex surgical intervention primarily used to treat pancreatic cancer and other periampullary malignancies. This procedure involves the removal of the head of the pancreas, along with portions of the duodenum, bile duct, and occasionally part of the stomach[6]. Given the intricate nature of this operation and its potential for complications, understanding the influence of comorbidities such as MASLD on surgical outcomes is crucial.

This review aims to explore the intersection of MASLD and PD, and the prevalence of hepatic steatosis post-PD.

Metabolic Dysfunction-Associated Steatotic Liver Disease

MASLD prevalence is increasing in parallel with the obesity epidemic and metabolic syndrome[2]. Recent epidemiological studies estimate notable variations across different regions and ethnicities[7,8].

The rising prevalence of MASLD is closely associated with several well-established risk factors. Obesity, particularly central adiposity, is the most significant contributor, with studies showing that up to 90% of severely obese individuals may have some degree of hepatic steatosis. Type 2 diabetes mellitus is another major risk factor, with an estimated 55-70% of patients with type 2 diabetes also having MASLD. Other important risk factors include insulin resistance, dyslipidemia, and metabolic syndrome [2,3,9].

Genetic factors also play a crucial role in MASLD susceptibility[10]. Genome-wide association studies have identified several genetic variants associated with increased risk, including PNPLA3, TM6SF2, and MBOAT7 (**Figure 1**) [11–13]. These genetic factors may explain the variability in MASLD prevalence and severity among different ethnic groups.

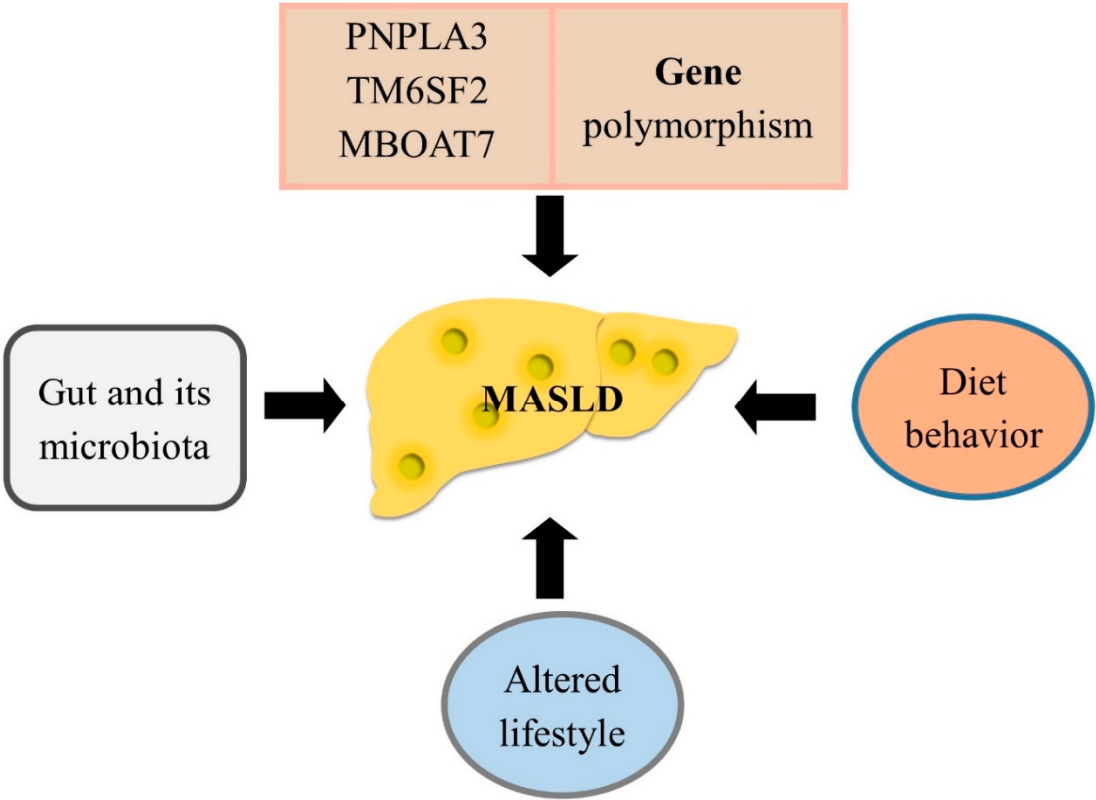


Figure 1. Factors which plays crucial role in MASLD susceptibility.

Age and sex are additional factors influencing MASLD prevalence[14]. The condition is more common in older individuals, with a peak prevalence typically observed in the fifth to sixth decades of life[15,16]. While earlier studies suggested a higher prevalence in men[17], recent data indicate that postmenopausal women may be at increased risk, possibly due to hormonal changes affecting lipid metabolism[18].

MASLD encompasses a spectrum of liver pathology, ranging from simple steatosis to more advanced stages characterized by inflammation, fibrosis, and ultimately cirrhosis[19]. The progression of MASLD is typically described in several stages, including simple steatosis, steatohepatitis, fibrosis, and cirrhosis [19–21].

Simple Steatosis is initial stage and is characterized by excessive fat accumulation in hepatocytes, typically affecting more than 5% of liver cells. While often considered benign, recent evidence suggests that even simple steatosis may not be entirely innocuous[22,23].

Steatohepatitis involves hepatic fat accumulation accompanied by inflammation and hepatocyte injury[24]. It is characterized histologically by ballooning degeneration of hepatocytes, inflammatory infiltrates, and often the presence of Mallory-Denk bodies[25,26].

Progressive inflammation and cellular injury lead to the activation of hepatic stellate cells and the deposition of extracellular matrix, resulting in fibrosis[27]. The degree of fibrosis can range from mild (stage F1) to severe (stage F4 or cirrhosis) [28].

Cirrhosis is the most advanced stage of MASLD, characterized by extensive fibrosis, distortion of the liver architecture, and impaired liver function [29]. Cirrhosis significantly increases the risk of hepatocellular carcinoma and liver failure [30].

The progression of MASLD is not linear, and not all individuals with simple steatosis will progress to more advanced stages. Factors influencing disease progression include the severity of metabolic dysfunction, genetic predisposition, and lifestyle factors such as diet and physical activity [31,32].

Recent research has also highlighted the dynamic nature of MASLD progression, with the potential for disease regression, particularly in earlier stages, through lifestyle modifications and improved metabolic control[33,34]. However, once significant fibrosis has developed, the potential for reversal becomes more limited[35].

Overview of Pancreaticoduodenectomy

Pancreaticoduodenectomy remains one of the most complex and challenging abdominal surgeries performed today (**Figure 2**) [6]. This intricate operation involves the removal of the head of the pancreas, the duodenum, the gallbladder, and part of the bile duct, followed by a complex reconstruction of the gastrointestinal tract[36]. Recent advances in surgical techniques, including minimally invasive approaches, have improved outcomes and expanded the procedure's applicability[37,38]. A 2024 meta-analysis by Tang et al. demonstrated that robotic PD is associated with reduced blood loss and shorter hospital stays compared to open surgery, albeit with longer operative times[39].

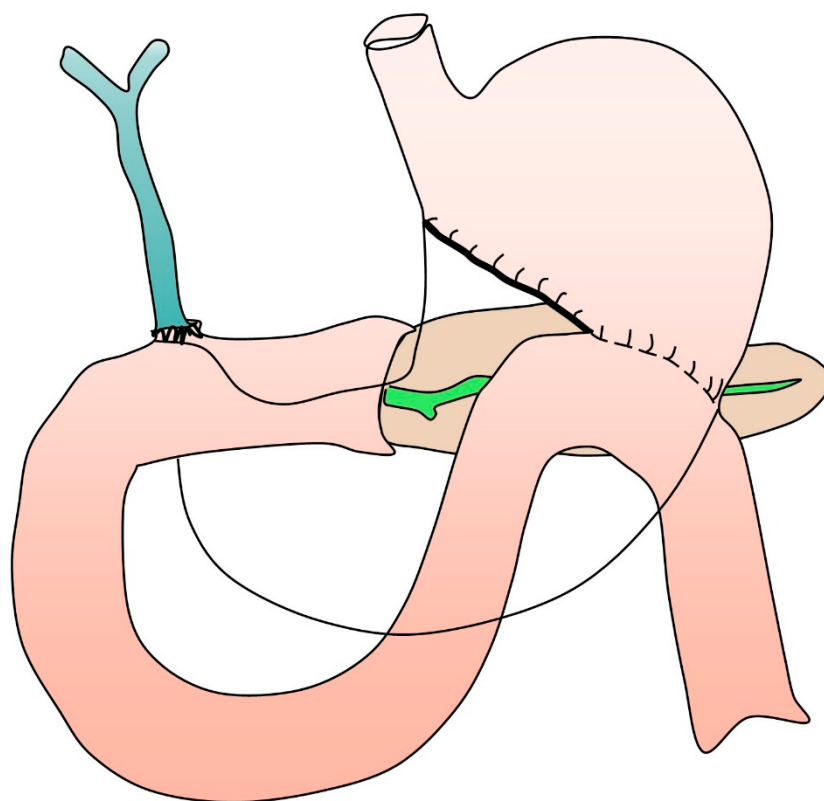


Figure 2. The pancreaticoduodenectomy surgery procedure.

The primary indication for PD remains the treatment of malignant neoplasms of the pancreatic head, distal common bile duct, and periampullary region[40]. However, its application has expanded to include select benign conditions such as chronic pancreatitis and intraductal papillary mucinous neoplasms (IPMNs) with high-risk features[41]. Studies highlighted the importance of precise patient selection, showing that adherence to evidence-based criteria for resection of IPMNs can significantly reduce unnecessary surgeries while maintaining oncological safety[42,43].

Despite advancements in surgical techniques and perioperative care, PD is associated with significant morbidity[44]. The most dreaded complication remains postoperative pancreatic fistula (POPF), occurring in 5-30% of cases and potentially leading to life-threatening sequelae[45,46]. A study demonstrated that transpapillary pancreatic duct stenting did not significantly reduce the rate of clinically relevant POPF in patients[47]. Other common complications include delayed gastric emptying, postpancreatectomy hemorrhage, and surgical site infections[48,49]. Recent data from high-volume centers report mortality rates below 5%, with five-year survival rates for pancreatic adenocarcinoma improving to 20-30% in selected patients, particularly those receiving multimodal therapy[50,51].

The landscape of PD continues to evolve, with ongoing research focusing on personalized approaches to patient care. Studies explored the use of circulating tumor DNA (ctDNA) analysis for early detection of recurrence following PD, potentially allowing for more timely interventions [52–55]. Additionally, the integration of artificial intelligence in preoperative planning and intraoperative decision-making is an exciting frontier[56,57]. The potential of machine learning algorithms to predict POPF risk with higher accuracy than traditional scoring systems, paving the way for tailored perioperative management strategies[58–61].

MASLD in Patients After Undergoing Pancreaticoduodenectomy

The precise etiology of steatotic liver disease following PD remains elusive; however, researchers have postulated that postoperative malnutrition, stemming from pancreatic exocrine insufficiency, may be a contributing factor[62]. Isolated cases of hepatic failure secondary to steatohepatitis have been documented as a potential complication following PD, though such occurrences are infrequent[63].

The prevalence of MASLD in patients who have undergone PD has garnered increasing attention in recent years, as the metabolic consequences of this complex surgery become more apparent.

The development and impact of MASLD following pancreatic surgery, particularly PD, have garnered attention due to significant implications for patient outcomes. Tanaka's findings underline a 23% prevalence of MASLD in patients post-PD, observing that non-obesity and absence of hyperlipidemia characterize this form of MASLD. A crucial association with pancreatic exocrine insufficiency was noted, with pancreatic enzyme supplementation significantly reducing steatosis and restoring biochemical balance. This suggests that pancreatic enzyme insufficiency may be a vital contributor to MASLD after PD and highlights the potential of enzyme therapy as a targeted intervention for patients with post-PD MASLD[64].

Expanding on this, Kato et al. [65] documented MASLD incidence at 19.6% following total pancreatectomy (TP), identifying female sex, elevated BMI, and postoperative diarrhea as independent risk factors. In Kato's study, MASLD resolved spontaneously in 37.9% of patients within a year, indicating a potential self-limiting course in certain cases. This variation in disease trajectory emphasizes the need to consider individual patient risk profiles and demonstrates that postoperative MASLD may differ in severity and duration depending on specific patient factors [65].

Nakagawa's study reported a MASLD incidence of 25% after PD, underscoring that postoperative pancreatic exocrine insufficiency (PEI) is the sole independent risk factor for MASLD. The correlation between MASLD incidence and low liver-to-spleen CT attenuation ratios suggests that imaging markers may serve as valuable predictors for MASLD in patients undergoing PD. These findings echo Tanaka's results and underscore PEI as a crucial factor, potentially necessitating more consistent and rigorous management of enzyme replacement postoperatively[66].

In efforts to predict MASLD risk, Kato et al. proposed a postoperative scoring system, identifying pancreatic adenocarcinoma and postoperative diarrhea as significant predictors. Kato's system correlates higher scores with increased MASLD prevalence (up to 93% for scores of 7–10), supporting a preventative approach by highlighting patients who would benefit most from nutritional intervention. This proactive strategy is especially relevant, as these patients are at higher risk of progressing from MASLD to NASH, complicating recovery and increasing liver disease burden[67].

Huang and colleagues emphasized that MASLD can disrupt essential adjuvant chemotherapy in cancer patients, with MASLD patients experiencing higher chemotherapy discontinuation rates (55.9%) than non-MASLD patients. This underscores MASLD's significant clinical impact, particularly in cancer patients, where treatment delays can adversely affect prognosis. Huang's findings reinforce the need for integrated management strategies addressing both MASLD prevention and continuity of cancer therapy to optimize patient outcomes post-surgery[68].

Additionally, Fujii's radiomics-based study highlights preoperative CT-derived radiomic features as potential predictors for MASLD post-PD. By incorporating both clinical and radiomic parameters, Fujii's predictive model achieved higher precision (72.7%) and recall (66.7%) than a solely clinical model, suggesting that advanced imaging techniques could improve MASLD risk stratification. This radiomics approach represents a step towards personalized risk assessment, allowing for targeted preventive measures in high-risk patients[69].

In a Belgian cohort, D'Cruz reported a 31% MASLD prevalence post-pancreatic surgery, with persistent cases observed up to two years postoperatively. The study linked MASLD occurrence to preoperative liver enzyme levels and weight loss, suggesting that long-term follow-up is essential[70]. These findings underscore that MASLD can present as both an early and late complication, necessitating prolonged monitoring and potential intervention to mitigate its progression and impact on liver function.

In a recent study by Shibata et al.[71], the incidence and clinical characteristics of hepatic steatosis following pancreatectomy, researchers have shed light on this growing concern in post-operative care. The study, which involved 104 patients who underwent pancreatic surgery, revealed that 20% of participants developed hepatic steatosis postoperatively. Notably, the research identified several risk factors for the development of hepatic steatosis, including a low neutrophil-to-lymphocyte ratio (NLR) in the overall cohort, and younger age, higher lymphocyte-to-monocyte ratio, and lymph node metastasis specifically in patients who underwent pancreaticoduodenectomy. These findings suggest a potential link between immune-nutritional parameters and the risk of postoperative hepatic steatosis, which could have significant implications for patient monitoring and management. The study also evaluated the effectiveness of pancrelipase administration at 900mg/day as a treatment for hepatic steatosis, with promising results. While some patients improved with dose escalation, others showed improvement without it, indicating that individualized treatment approaches may be necessary. However, it is important to note that the sample size for this aspect of the study was relatively small, and further research with larger cohorts is needed to confirm these findings and establish optimal dosing strategies for pancreatic enzyme replacement therapy in preventing and treating postoperative hepatic steatosis.

Izumi's study emphasizes the impact of postoperative body mass index (BMI) and pancreatic cancer on the risk of MASLD following PD. The study's data, which includes 101 patients, reveals that a lower postoperative BMI is linked to fat deposition (Hazard ratio (HR) of 0.56, $p = 0.042$), while pancreatic cancer presents as a strong risk factor for MASLD (HR 4.42, $p = 0.034$)[72]. These findings highlight how weight management and cancer-associated metabolic stress can exacerbate liver complications after PD, suggesting that BMI maintenance might serve as an important focus in postoperative care.

Fujii's research identifies additional risk factors over time, examining a larger cohort of 196 patients and revealing that MASLD prevalence varies postoperatively: 12% at one month, rising to 21% at six months, then slightly dropping to 15% at one year. Significantly, female patients with decreased serum copper (Cu) appear to be at a higher risk across these time points, suggesting that

micronutrient deficiencies and gender-specific responses to pancreatic exocrine insufficiency may drive MASLD progression. Fujii's emphasis on copper reduction aligns with broader studies on micronutrient impacts on hepatic function, indicating that serum Cu levels could be monitored to identify at-risk groups[73].

Yoo's study further distinguishes hepatic steatosis patterns, reporting a notable difference in MASLD occurrence between patients undergoing pylorus-preserving PD (PPPD) and those with bile duct resections (BDR). While PPPD patients showed a five-year MASLD incidence of 26.7%, BDR patients had only a 3.7% incidence ($p < 0.001$). Yoo's findings suggest a link between the surgical technique and the sustained incidence of MASLD, indicating the need for multicenter studies to better understand the pathophysiological mechanisms behind these observed differences[74]. The persistence of MASLD in the PPPD cohort hints that PPPD may lead to prolonged changes in hepatic metabolism, possibly due to altered bile acid regulation or extended digestive changes.

Yu's work on CT liver attenuation post-PD adds valuable insights into radiological changes associated with MASLD. Observing a significant decline in liver attenuation (from 52.3 to 47.6 Hounsfield units, $p = 0.044$) and a reduced liver-to-spleen attenuation ratio (1.12 to 1.01, $p = 0.033$), Yu suggests that these imaging biomarkers could serve as early indicators of MASLD onset post-PD[75].

Lastly, Ito's findings spotlight intraoperative blood loss as an independent risk factor for MASLD development post-PD, with blood loss correlating strongly with the incidence of steatohepatitis (HR = 1.0001, $p = 0.016$)[76]. This critical link between surgical blood loss and MASLD risk underscores the importance of intraoperative management. Collectively, these studies underscore the multifactorial nature of MASLD post-PD, with risk factors spanning surgical, demographic, nutritional, and metabolic domains. Future studies could prioritize exploring the interactive effects of these variables, aiming to develop comprehensive MASLD prevention strategies for post-PD patients.

In an examination of MASLD in patients after pancreatoduodenectomy, recent findings have shed light on the prevalence, risk factors, and potential management strategies for this condition. A retrospective study of 120 patients who underwent pancreatoduodenectomy revealed a high occurrence rate of MASLD, with 38% of patients developing the condition postoperatively. Notably, the study identified several independent risk factors for MASLD development, including high body mass index, small pancreatic volume, prolonged operative time, and elevated aspartate aminotransferase/alanine aminotransferase ratio one month post-surgery. These findings underscore the importance of careful patient selection and perioperative management to mitigate the risk of MASLD. Interestingly, the study also explored the potential benefits of pancreatic enzyme supplementation therapy, suggesting a trend towards lower MASLD occurrence in patients receiving prophylactic supplementation (27% vs. 43%, $p = 0.082$). Furthermore, the recovery rates from MASLD were notably higher in patients receiving pancreatic enzyme supplementation therapy compared to those who did not (100% vs. 58%, $p = 0.069$), although the small sample size warrants cautious interpretation. The identification of predictive factors for MASLD recovery, such as small diameter main pancreatic duct and low serum amylase levels at postoperative day 28, provides valuable insights for tailoring postoperative management strategies. While these findings offer promising directions for clinical practice, further prospective studies with larger cohorts are necessary to validate these results and establish definitive guidelines for the prevention and management of MASLD in post-pancreatoduodenectomy patients[77].

In an examination of postoperative hepatic steatosis following total pancreatectomy, recent findings have shed light on the complex interplay of factors contributing to this condition. The study revealed that a significant proportion (37.2%) of patients developed hepatic steatosis post-surgery, accompanied by notable declines in nutritional status and body mass index. Intriguingly, the research identified several key risk factors beyond the previously established association with remnant pancreatic function. Female sex emerged as a significant predictor, suggesting potential hormonal or metabolic influences that warrant further investigation. Additionally, early postoperative serum albumin levels were found to be correlated with the development of hepatic steatosis, underscoring

the critical role of nutritional status in post-surgical liver health. Perhaps most notably, the study highlighted the potential preventive effects of high-dose pancreatic enzyme replacement therapy on postoperative hepatic steatosis. This finding not only emphasizes the importance of managing pancreatic exocrine insufficiency but also opens up new avenues for targeted interventions to mitigate the risk of hepatic steatosis in pancreatectomized patients. While these results provide valuable insights, it is important to note that the study's relatively small sample size and focus on total pancreatectomy patients may limit its generalizability to other pancreatic surgeries. Future research should aim to validate these findings in larger, more diverse cohorts and explore the long-term implications of these risk factors and potential preventive strategies[78].

Collectively, these findings illustrate that MASLD is a prevalent and impactful complication following PD and TP, with a multifactorial etiology linked to PEI, patient demographics, and treatment factors. Improved predictive strategies, enzyme replacement therapy, and tailored postoperative care emerge as pivotal in managing MASLD, helping mitigate its impact on liver function and patient recovery trajectory.

Conclusion

In conclusion, this review underscores the significant interplay between MASLD and PD, highlighting a relationship that impacts postoperative outcomes. The prevalence of MASLD in patients undergoing PD presents unique challenges, influencing surgical decision-making and necessitating tailored perioperative management strategies. Moreover, the emergence of MASLD following PD introduces long-term metabolic and hepatic consequences that warrant close monitoring and proactive intervention.

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Authors' Contributions: MS: Reviewing the literature, Methodology, Investigation, Conceptualization, Data curation, Formal analysis, Writing – the original draft, review & and editing, Designing the Figures.

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