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**Metabolic syndrome and non-alcoholic fatty liver disease in liver surgery: The new scourges?**

Cauchy F *et al.* Metabolic disorders and liver surgery

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**Abstract**

The aim of this topic highlight is to review relevant evidences regarding the influence of the metabolic syndrome (MS) and its associated liver manifestation, the non-alcoholic fatty liver disease (NAFLD), on the development of liver cancer as well as their impact on the results of major liver surgery. MS and NAFLD, whose incidences are significantly increasing in Western countries, are leading to a changing profile of the patients undergoing liver surgery. A MEDLINE search was performed for relevant articles using the key words "metabolic syndrome”, “liver resection", “liver transplantation”, "non alcoholic fatty liver disease", “non-alcoholic steatohepatitis”, and "liver cancer". On one hand, the MS favors the development of primary liver malignancies (hepatocellular carcinoma and cholangiocarcinoma) either through NAFLD liver parenchymal alterations (steatosis, steatohepatitis, fibrosis), or in the absence of significant underlying liver parenchyma changes. Also, the existence of NAFLD may have a specific impact on colorectal liver metastases recurrence. On the other hand, the postoperative period following partial liver resection and liver transplantation is at increased risk of both postoperative complications and mortality. These deleterious effects seem to be related to the existence of liver specific complications but also higher cardio-vascular sensitivity in a setting of MS/NAFLD. Finally, the long-term prognosis after curative surgery joins that of patients operated with other types of underlying liver diseases. An increased rate of patients with MS/NAFLD referred in hepatobiliary units has to be expected. The higher operative risk observed in this subset of patients will require specific improvements in their perioperative management.

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**Key words:** Metabolic syndrome; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Neoplasia; Hepatocarcinoma; Liver surgery; Complications; Morbidity

**Core tip**: The metabolic syndrome (MS) and its hepatic manifestations, the non-alcoholic fatty liver disease (NAFLD), are increasingly observed in western countries. Both MS and NAFLD could favor the development of primary liver malignancies and may also lead to end-stage liver disease. These patients are at higher operative risk because of underestimated postoperative liver related complications but also specific increase in cardio-vascular complications. Specific improvements in the perioperative management of these patients are required in order to improve the operative results.

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**INTRODUCTION**

The prevalence of the metabolic syndrome (MS) is reaching epidemic levels in Western Europe and Northern America, where it is reported to be as high as 25% in the general population[1]. The MS is a constellation of clinico-biological features closely related to insulin-resistance and includes dyslipidemia, hypertension, glucose intolerance and central obesity[1]. Non-alcoholic fatty liver disease (NAFLD) represents the hepatic manifestation of the MS. NAFLD pathological alterations, which range from simple steatosis to steatohepatitis may lead to fibrosis and end stage liver disease[2]. As its incidence parallels that of the MS, NAFLD is currently becoming one of the first chronic liver diseases in Western countries and therefore has a major health impact[3]. Also, both MS and NAFLD have been suggested to be directly or indirectly associated with the development of primary liver malignancies[4-7]. For all these reasons, it is likely that more and more of these patients will be referred in hepatobiliary (HPB) and liver transplant units in upcoming years[8].

The increasing prevalence of MS/NAFLD and MS/NAFLD-related liver tumors is not the only issue related to these disorders. Despite numerous advances in the fields of hepatology, perioperative management and liver surgery, the impact of both MS and NAFLD on the postoperative course of patients undergoing liver surgery has long been neglected. As a matter of fact, it’s only recently that evidences suggesting a specific and underestimated risk regarding postoperative morbidity and mortality in the setting of liver surgery have been released[8-13]. In that sense, it seems crucial that gastroenterologists and surgeons should be fully aware of the existence of MS and NAFLD as well as their negative impact on the postoperative course in order optimize the peri-operative management of concerned patients and to prevent any avoidable morbidity/mortality.

The objectives of this review are therefore: (1) to provide comprehensive insights regarding the current standards and issues in the diagnosis of both MS and NAFLD; (2) to clarify their respective impact on tumor progression as well as their influence on postoperative outcome; and (3) to discuss the measures, which should be undertaken in upcoming years in order to improve the results of surgery.

**DEFINITIONS AND ISSUES**

***Metabolic syndrome***

The definition of MS has evolved during the past decade. Current consensual criteria for its diagnosis are summarized in Table 1. These include central (or android) obesity, hypertension, dyslipidemia, with either increased triglycerides level or decreased high density lipoprotein cholesterol level, and glucose intolerance[1]. Even-though, the presence of at least 3 out of 5 criteria of the consensual definition are required to define the MS[1] both liver histological manifestations and influence on surgical outcomes after liver surgery may occur in patients presenting with individual components of the MS. Indeed, fatty liver disease may also occur in patients with isolated diabetes mellitus (DM)[14], hypertriglyceridemia[15] and obesity[16,17]. Likewise, higher perioperative morbidity or mortality rates after liver resection are reported in patients with only DM[18,19] or overweight/obesity[20,21], whereas our groups found the association of just 2 disorders to be related to poor outcome of surgery[13,22] .

Interestingly, most of the medical and surgical studies do not always gather all these consensual criteria but rather use substitutes for convenience. Such substitutes may lead to a certain degree of confusion. For example, it is frequently assumed that patients receiving statin or fenofibrate medication have dyslipidemia[8,11] and that patients receiving antihypertensive therapy have hypertension. However, some of these patients may receive such medications for primary cardiovascular prevention or renal protection. In the same way, central obesity, which reflects visceral adiposity, it is often measured using the BMI and various cut off values are proposed[8,12,13]. Yet, BMI does not allow distinguishing central obesity, which is a metabolic disorder included in the MS, from peripheral obesity. In that sense, circumferential waist appears to be more reliable and should be preferred[23,24]. Finally, the terms hyperglycemia and insulin-resistance are often used indiscriminately, whereas some authors suggest that they should not. Hence, the presence of insulin-resistance should be routinely assessed using the homeostasis model assessment of insulin resistance (HOMA-IR)[25] whenever hyperglycemia is found.

***NAFLD***

NAFLD has emerged as one of the most frequent forms of chronic liver disease in Western countries[5,6] and should be considered in case of fatty infiltration exceeding 5% of the liver parenchyma at histology in the absence of previous or ongoing significant alcohol consumption[26]. Although NAFLD is considered the hepatic manifestation of the MS, other conditions including chronic hepatitis B and C infection[27,28], irinotecan based chemotherapy[29,30] and several other medications including methotrexate, tamoxifen or amiodarone[31,32] may also lead to fatty liver disease and should be meticulously ruled out. NAFLD, which encompasses a wide spectrum of diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH)[26], can progress to cirrhosis and may lead to end-stage liver disease[5,6]. Histological analysis remains the gold standard for the assessment of NAFLD and should be performed by a trained pathologist[33]. Several histological scores might be useful for diagnosis. The most frequently used score is the non-alcoholic liver disease activity score (NAS) proposed by Kleiner *et al*[26], which is a semiquantitative, histology-based score system including three parameters, namely steatosis (on a scale of 0-3), lobular inflammation and hepatocellular ballooning (on a scale of 0-2 each) and therefore ranges from 0 to 7. Likewise, Bedossa *et al*[34] recently published a histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients.

***NASH***

NASH is considered the result of long-lasting inflammation. It is characterized by several histological alterations, including steatosis, lobular inflammation, ballooning and may also be associated with fibrosis. Even though the diagnosis of NASH was initially suggested for NAS values of 4 or 5[26], there is an ongoing debate regarding the accuracy of NAS in assessing NASH. Interestingly, Brunt *et al*[33] have emphasized that the diagnosis of NASH based on evaluation of patterns as well as individual lesions on liver biopsies did not always correlated with threshold values of the semi quantitative NAS. Moreover, NAS does not include other histologic alterations often present in NAFLD, such as microcirculation modifications, which are not routinely reported by pathologists[35]. Thus, rather than being based on the NAS value alone, the differentiation between NASH and no-NASH should rather take into account the pathologist report[33].

***Identification of NASH in patients with MS/NAFLD***

Since the increasing incidence of both MS and NAFLD in Western populations de facto put a great amount of patients at risk of developing NASH, any large scale screening policy aimed to obtain histological diagnosis of NAFLD does not seem reasonable. Furthermore, the accuracy of histology in identifying NASH is suboptimal as both inter-observer variations[36] and discrepancies from one sample to the other within the same parenchyma may occur[37]. In order to increase cost/effectiveness and accuracy of diagnosis, and also to avoid the intrinsic invasiveness of biopsy, there has been significant interest in identifying non-invasive methods of predicting liver histology in patients with suspected NASH. Hence, numerous biological (alanine aminotransferase/aspartate aminotransferase ratio, FIB-4, analysis of organic compounds in breath)[38], and imaging techniques [magnetic resonance imaging (MRI) for quantification of liver steatosis[39] or magnetic resonance spectroscopy) have been proposed for the detection of underlying parenchymal changes among patients with MS, but none has become the “gold standard”. In particular, although MRI has shown high accuracy in detecting steatosis, its effectiveness in evaluating (and possibly ruling out) fibrosis is questionable in the presence of fat[40].

**MS/NAFLD INFLUENCE ON CARCINOGENESIS.**

The association between individual components of the MS such as diabetes[41] and overweight[42], and an increased risk of cancer has long been known. More recently, it has been suggested that the MS itself was implicated in carcinogenesis, especially in the liver[4]. Indeed, two recent series have shown that the MS itself was associated with an increased risk of developing of both HCC[3] and intrahepatic cholangiocarcinoma[43]. In particular, HCC incidence in patients with MS is reportedly 2-4 fold higher than in general population[7].

How the MS acts to promote carcinogenesis remains to be fully elucidated. Several genetic mechanisms are supposed to be involved in MS-related carcinogenesis. First, direct oncologic effects may play a role in the carcinogenesis by loss of tumor suppression genes, deregulation of IL-6 signal or inhibition of JNK1 phosphorylation[22]. This mechanism is supposed to be at the origin of malignant transformation of liver cell adenoma in men[44]. Second, the MS has been reported to be associated with low-grade, chronic systemic inflammation, implying a serum increase of inflammatory cytokines such as TNF-α and IL-6[5] and a decrease in anti-inflammatory ones including adipocytokines[45].

Interestingly, most studies focusing on HCC occurring in patients with MS (or arising in a context of NAFLD) have consistently reported that 30%-60% of the patients displayed no feature of severe underlying fibrosis[7,8,22,46]. More surprisingly, almost 20% of the patients had a normal underlying liver parenchyma after conventional pathological examination. In this setting, HCCs furthermore tended to be isolated and of large-size[8,22]. These findings seem to indicate that several different pathways may be implicated in liver carcinogenesis in patients with MS as suggested by the inconstant presence of various histology alterations.

Although not always present, NASH related cirrhosis may be possibly considered a precancerous lesion, as it is associated with a yearly incidence of HCC as high as 2.6%[5] leading to a cumulative 5-year incidence ranging from 7.6%[47] to 11%[48]. In the event of NASH related cirrhosis, both presence and pattern of hepatic iron deposition[49] have been incriminated to further accentuate parenchymal changes thus promoting liver carcinogenesis.

Virus infection may also play an indirect role in tumor development in patients with MS. In particular, the specific subset of patients with chronic hepatitis C virus (HCV) infection developing an HCC is worth to be mentioned. Several authors have emphasized that chronic HCV infection was associated with fatty infiltration of the liver parenchyma in 50%-70% of the cases, including massive steatosis and NASH[27,28,50,51]. A non-negligible number of these latter display the so-called “viral steatosis” as a consequence of virus interference with fat metabolism (in the absence of pre-existing metabolic disorders). Thus, in this setting, steatosis itself could be responsible for the occurrence of secondary insulin-resistance and systemic inflammation. Even though the “viral steatosis” has been shown to regress after viral eradication[52], its existence has been incriminated in recurrence of HCV related HCC[53] after curative surgery. However, since steatosis and lobular inflammation may be found in HCV infection regardless of MS/NAFLD, the supposed association between HCC, HCV and NAFLD could be more a statistical artifact than a real oncogenetic mechanism. Taken together, the supposed pathway from viral infection to viral steatosis and HCC, as well as the possible mechanisms finally leading to HCC development (fibrosis, inflammation or induced insulin-resistance), still remain to be assessed.

Finally, the association between MS, NAFLD and colorectal liver metastases (CLM) has to be considered. Indeed, whereas several studies on colorectal cancer patients analyzed the impact of 5FU + irinotecan based chemotherapy on the development of steatohepatitis[28,30], it’s only recently that studies have focused on the specific oncologic influence of both MS and NAFLD on CLM, with various results. On one hand, Hamady *et al*[54] found that liver steatosis was associated with a 1.3 fold risk of local recurrence following liver resection for CLM, regardless of the chemotherapy regimen used. On the other hand, Viganò *et al*[55] studying the impact of chemotherapy-related liver injuries, pathological tumor regression grade, and micrometastases on long-term survival, have found that higher grade (2-3) steatosis was significantly associated with improved 5-year-overall survival compared to lesser steatosis (grade 0-1) after resection of CLM (52.5% *vs* 35.2%, *P* = 0.002). Even though these studies lacked specific histological assessment of NAFLD and precise identification of metabolic disorders, the observed results clearly reflect the growing enthusiasm of surgeons in exploring the impact of NAFLD on the long-term outcomes of patients with CLM.

**MS/NAFLD IMPACT ON OUTCOME OF LIVER SURGERY**

The impact of individual components of the MS and liver steatosis on the postoperative course following liver resection has been extensively investigated[18,56-60]. Accordingly, it has been established that liver surgeryprovided poorer results in patients affected by diabetes[18] or obesity[56,57] than in otherwise healthy patients. Similarly, several studies have highlighted that steatosis per se was a risk factor for postoperative complications after major hepatectomy[58-60]. In experimental models, liver fatty infiltration such as mild or severe steatosis has been found to be associated with lower regenerative ability following portal vein occlusion, elevated sensitivity to ischemia-reperfusion injury and higher hepatocellular injury after partial liver resection[61]. Nevertheless, it’s only recently that surgeons have focused on the results of surgery, liver resection and transplantation, in the specific subset of patients with MS or NASH.

***Liver resection***

Table 2 summarizes the results of recent series analyzing the early outcome of patients undergoing liver resection in a setting of MS/NASH[8-13].Of these six series, three aimed at assessing the influence of the MS on outcome[8,12,13], whereas the remaining three aimed at evaluating the impact of histological modifications, including NAFLD and NASH[9-11]. The fact that data concerning metabolic disorders (and MS) and liver histology were gathered together in only half of the series[8,11,13] emphasizes the absence of clear understanding of the relationship between MS and MS-related liver disease. In these studies, mortality after liver resection varied from 3% up to 30%, and was related to the primarily studied parameter, *i.e.,* MS, NAFLD or NASH. In this setting, it has been recently suggested that MS patients with a NAS > 2[8] or those with an histological diagnosis of NASH[11] had a 2.7-fold risk of experiencing liver related but also cardio-respiratory complications than those with normal underlying parenchyma. Hence, it seems that steatohepatitis rather than simple steatosis was a risk factor for postoperative complications[11]. Even if these recent findings may appear in opposition with previously published results maintaining a negative impact of steatosis on outcome[58-60], it is likely that the poor assessment of inflammatory changes in the underlying steatosic parenchyma may have biased older series. On the opposite, the progressive increasing degree of parenchymal change, damage and inflammation from steatosis to steatohepatitis is nowadays considered as a continuum, which progressively and proportionally increases overall postoperative morbidity/mortality.

Intuitively, not only the “quality” but also the “quantity” of liver remnant should be considered. In fact, it has been recently suggested that NASH was independently associated with both higher postoperative liver insufficiency and mortality following right hepatectomy (including extended right hepatectomy)[13], and trisectionectomy[10], although a (usually) “safe” amount of liver parenchyma was left in place. This result clearly emphasizes the worse tolerance to extended resection of fatty and inflammatory livers. This feature may be of particular importance in the case of HCC developing in a MS/NAFLD context, where large lesions often require major resections[8,22].

Considering cardiovascular morbidity/mortality, it has been shown that NASH was an independent risk-factor for the development of coronary artery disease and calcifications regardless the degree of visceral adiposity[62,63], thus leading to higher incidence of cardio-respiratory events following liver resection. Possibly, the recently described hemorheological alterations occurring in MS patients, including increased erythrocyte aggregation[64,65], may play a role in ischemic cardiac events.

***Liver transplantation***

NASH can progress to cirrhosis[2,4] and may lead to end-stage liver disease requiring liver transplantation (LT). During the last decade, the rate of LT performed for NASH related end-stage liver disease has dramatically increased from about 3% in the early 2000’s up to 19% in 2011[2]. Currently, non-alcoholic steatohepatitis is the third most common cause of LT in the US and is on the pace to become the most common within the next two decades in Western countries[66].

LT in NASH patients has peculiar aspects. Compared with other patients undergoing LT, recipients with NASH tend to be older[67] and obviously have a higher frequency of metabolic disorders[62]. In this setting, procedures significantly last longer and are associated with higher blood loss and longer post-transplantation hospital stay[62]. Accordingly, 30-d mortality after LT in patients with NASH tends to be higher than that for other indications[68]. Several studies have reported increased liver related morbidity rates in NASH patients, such as acute rejection rates[67] but also extra-hepatic complications, including sepsis and renal dysfunction[69]. Similarly to patients undergoing liver resectional surgery, NASH patients also have a higher likelihood of developing cardio-vascular complications after LT[62,67,69]. These events, which mainly occur within the first year after LT, have been reported to be responsible for as high as 50% of the total mortality following LT[62]. The relationship between MS/NASH and cardiovascular morbidity seems more complex than a generic multi-organ vascular disorder due to MS, as suggested by the significantly higher occurrence of cardiovascular events associated to MS whenever NASH is present[70]. In fact, similarly to what has been observed after LR, NASH is nowadays thought to put patients at an even higher risk of cardio-vascular complications, regardless of comorbidities and patient-specific cardiac risk[62]. Here again, it is likely that the degree of inflammation in the underlying liver represents a key factor in the occurrence of increased cardiovascular sensitivity.

Long-term results of LT following transplantation for NASH are encouraging. One, three and five-year survivals after LT for NASH ranges from 84%-87.6%, 75%-82.2% and 70%-76.7%, respectively, and are at least similar to that observed for LT for other traditional indications[2,62,67,68,71]. Even more remarkable, LT for HCC developed in patients with NASH seems to provide excellent long-term outcome with higher survivals compared with patients transplanted for HCV related HCC[72]. These observations could be the result of less aggressive tumors in NASH patients with lower micro vascular invasion and decreased rates of poorly differentiated lesions[8,72].

LT in patients with NASH related cirrhosis presents peculiar issues, including cirrhosis recurrence, to be discussed separately. Recurrent disease after LT for NASH related cirrhosis has been reported to occur in as high as 34% of recipients[68,73]. There is little information detailing the occurrence and histological evolution of NAFLD recurrence after LT, and the long-term natural history of NAFLD recurrence itself is unclear[74]. Nevertheless, in these patients, recurrence is often associated with the presence of the MS or its individual components[73]. Accordingly, recurrence should be further evaluated in larger studies, with special emphasis on management of MS and secondary prevention strategies[73].

**WHICH IMPROVEMENTS SHOULD BE UNDERTAKEN IN UPCOMING YEARS?**

Both MS and NAFLD/NASH adversely affect short and long-term results of liver surgery. Considering that the rate of patients presenting with such conditions will keep on increasing in upcoming years, it appears crucial that specific measures should be undertaken in order to improve those unsatisfactory results. Above all, the worse tolerance to extended resection of fatty and inflammatory livers (as a consequence of lower regenerative ability), requires that this issue should be attentively pondered in the preoperative planning of surgical strategy whenever a major resection is needed. Unfortunately, the culture of considering just MS or steatosis (even without liver biopsy confirmation) a potential risk factor for major surgery has not already entered clinical practice even in specialized environments. Addressing this issue, our group has recently shown that MS patients operated for HCC less frequently underwent preoperative PVE when they displayed a NAS > 2 without severe fibrosis compared to those with severe underlying fibrosis, suggesting that these latter patients would probably benefit of a better anticipation of their operative risk, especially in case of planned major LR[8].

In general, preventing measures to reduce MS/NAFLD related morbidity/mortality should include: (1) better characterization of the underlying parenchyma using invasive or non-invasive means knowing that patients with inflammatory fatty liver even without severe fibrosis are at similar operative risk as those with severe underlying fibrosis; (2) targeted perioperative management including complete preoperative cardio-vascular work-up and intra-operative cardio-vascular and pulmonary monitoring; and, finally; and (3) specific, “NAFLD-tailored” peri-operative surgical care, such as parenchymal sparing resections, wide use of liver volume modulation techniques, including portal vein embolization and portal vein ligation, but also targeted medical therapies developed in order to improve the tolerance to LR. Concerning this latter issue, a recent experimental study has highlighted the benefits of omega-3 acids in reducing severe steatosis in a preoperative setting leading to improved liver regeneration and functional recovery following partial hepatectomy[75]. These encouraging preliminary results yet require confirmation in a clinical setting but may already be considered a promising future field of research.

Concerning the relationship between MS/NAFLD and neoplastic disease, several strategies should be developed in order to prevent both occurrence and recurrence of primary liver cancer in MS/NASH patients. Even though it is generally recommended that overweight and obese patients with NAFLD lose 7%-10% of their body weight by dietary modification and exercise over the course of 6-12 months, the paucity of data makes it difficult to make evidence-based recommendations about dietary modification and exercise to treat NAFLD and NASH[76]. In fact, medical research has mainly focused on reducing NASH in MS patients using medical therapies. Several randomized controlled trials have shown significant downstaging of NASH following the administration of specific medications, including vitamin E and pioglitazone[77-79]. Retrospective studies have shown that the use of biguanides, such as metformin, was associated with HCC risk reduction among diabetic patients[80,81]. Experimentally, metformin has been shown to provide antineoplastic effects through deregulation of the m-TOR pathway[82,83]. Hence, in a context of MS/NAFLD related HCC, metformin would theoretically represent an ideal preventing therapy reducing both incidence of HCC following parenchymal alterations or systemic inflammation but also providing inherent antitumoral properties. Nevertheless, despite the encouraging results of all these medications and the possible future development of others even more effective, it should be kept in mind that none of them have currently been tested in a surgical context. In fact, the prolonged time interval required by medications to obtain relevant effects on liver parenchyma possibly reducing morbidity, definitely questions its applicability in a surgical environment prior to (or after) surgery. This considerations gains interest if one considers that the great majority of patients undergoing major liver surgery (LR and LT) presents with cancer or end stage liver disease, needing prompt management. Obviously, any medical/preventing strategy should ideally require a large-scale evaluation in a surgical setting.

**CONCLUSION**

Both the pro-oncogenic effect on the underlying liver and the rising incidence of MS/NASH imply that an increased number of patients with such condition referred to HPB units has to be expected. The higher operative risk observed in these patients can be partially explained by both underestimated liver related risk but also high peri-operative cardio-vascular and respiratory susceptibility. These unsatisfactory postoperative results will require targeted peri-operative management. Such actions are justified by the observed favorable long-term outcomes.

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**Table 1 Diagnostic criteria of the metabolic syndrome**

|  |  |  |
| --- | --- | --- |
| Criteria  | Consensual criteria definition1 | Other non-consensual criteria |
| Central obesity  | Abdominal waist2 | Different cutoff values of BMI≥28 or ≥ 28.8 or ≥ 30 kg/m2 |
| > 102 cm (United States) or 94 cm (Europe) in men |
| > 88 cm (United States) or 80 cm (Europe) in women |
| Dyslipidemia  | Triglycerides ≥ 150 mg/dL (1.7 mmol/L) | Statin or fenofibrate medication3 |
| HDL cholesterol  |
| < 40 mg/dL (1.03 mmol/L) in men |
| < 50 mg/dL (1.29 mmol/L) in women |
| Hypertension | Blood pressure >135/85 mmHg | Any antihypertensive therapy3  |
| Glucose intolerance | Hyperglycemia | Any diabetes Any antidiabetic therapy (oral or insulin)  |
| Fasting glucose ≥ 110 mg/dL, |
| or type II diabetes |

1Diagnosis of metabolic syndrome (MS) requires at least 3 out of 5 criteria; 2Other cut off values have been established for Asians and Latin Americans; 3These treatments can be taken in account for the diagnosis of MS unless if given in preemptive purpose.

**Table 2 Studies focusing on liver resection in a context of metabolic syndrome, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Ref. | Endpoint | Underlying parenchyma | Assessment of metabolic factors | Morbidity | Mortality |
| Overall | Liver related | CV and respiratory |
| Wakai *et al*[9] | Influence of the underlying liver on liver resection | NAFLD (*n =* 17) | BMI | 59% | 47% | 6% | 12% |
| Neal, *et al*[10] | Influence of the underlying liver on right trisectionectomy | NASH (*n =* 9) | All factors | NA | NA | NA | 22% |
| Reddy *et al*[11] | Influence of the underlying liver on liver resection | Simple steatosis (*n =* 72) NASH (*n =* 102) | All factors | 35%57% | 19%28% | 28%13% | 4%4% |
| Bhayani *et al*[12] | Influence of the MS on liver resection | NA | MS (*n =* 256)No MS (*n =* 3.717) | 29%23% | NA | 22%15% | 6%2% |
| Le Bian *et al*[13] | Influence of the MS on right trisectionectomy | NAFLD (*n =* 27) | >2 MS factors (*n =* 30)≥ 3 MS factors (*n =* 13) | 60%NA | 53%NA | NANA | 30%54% |
| Cauchy *et al*[8] | Influence of the MS on liver resection | NASH (*n =* 16) | MS (*n =* 62) | 58% | 21%1 | 17%1 | 11% |

1Major complications: Clavien III-V. MS: Metabolic syndrome; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; CV:Cardiovascular; NA: Not applicable.