

# A clinical perspective of the link between metabolic syndrome and hepatocellular carcinoma

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**Abstract:** Metabolic syndrome (MS), which is defined as a constellation of clinico-biological features closely related to insulin-resistance has reached epidemic levels in Western Europe and Northern America. Non-alcoholic fatty liver disease (NAFLD) represents the hepatic manifestation of MS. As its incidence parallels that of MS, NAFLD is currently becoming one of the most frequent chronic liver diseases in Western countries. On one hand, MS favors the development of hepatocellular carcinoma (HCC) either through NAFLD liver parenchymal alterations (steatosis; steatohepatitis; fibrosis), or in the absence of significant underlying liver parenchyma changes. In this setting, HCC are often diagnosed incidentally, tend to be larger than in patients developing HCC on cirrhosis and therefore frequently require major liver resections. On the other hand, MS patients are at increased risk of both liver-related postoperative complications and increased cardiorespiratory events leading to non-negligible mortality rates following liver surgery. These deleterious effects seem to be related to the existence of impaired liver function even in the absence of severe fibrosis but also higher cardiorespiratory sensitivity in a setting of MS/NAFLD. Hence, specific medical and surgical improvements in the perioperative management of these patients are required. These include complete preoperative cardiorespiratory work-up and the wide use of preoperative liver volume modulation. Finally, the long-term prognosis after curative surgery for MS-related HCC does not seem to be worse than for other HCC occurring on classical chronic liver diseases. This is probably related to less aggressive tumor behavior with lower micro vascular invasion and decreased rates of poorly differentiated lesions. In this setting, several medical therapies including metformin could be of value in the prevention of both occurrence and recurrence of HCC.

**Keywords:** metabolic syndrome, NAFLD, NASH, neoplasia, hepatocellular carcinoma, hepatectomy, complications, morbidity

## Introduction

The prevalence of metabolic syndrome (MS) has reached epidemic levels in Western Europe and Northern America, where it is reported to be as high as 25%.<sup>1</sup> MS is defined as a constellation of clinico-biological features closely related to insulin-resistance and includes dyslipidemia, hypertension, glucose intolerance and central obesity.<sup>1</sup> Non-alcoholic fatty liver disease (NAFLD) accounts for the hepatic manifestation of MS. NAFLD ranges from simple steatosis to steatohepatitis and may lead to fibrosis and end-stage liver disease.<sup>2</sup> As its incidence parallels that of MS, NAFLD has become one of the most frequent chronic liver diseases in Western countries.<sup>3</sup> Also, it has been suggested that both MS and NAFLD could directly or indirectly promote the development of primary liver malignancies.<sup>4-7</sup> Hence, it is likely that more and more of these patients will be referred in hepatobiliary and liver transplant units in upcoming years.<sup>8</sup>

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Despite increasing concerns regarding the growing incidence of MS/NAFLD-related liver malignancy, the specific impact of both MS and NAFLD on the postoperative course of patients undergoing liver surgery has long been neglected. Indeed, it is only recently that evidence suggesting an underestimated risk regarding postoperative morbidity and mortality in MS patients undergoing liver surgery has been released.<sup>8–13</sup> In that sense, clinicians should be fully aware that the existence of MS and NAFLD may have a negative impact on the postoperative course of their patients in order to optimize perioperative management and prevent avoidable morbidity/mortality.

The present review aims to provide comprehensive insights regarding the current standards and issues in the diagnosis of both MS and NAFLD in order to clarify their respective impact on tumor progression as well as their influence on the postoperative outcome. Finally, we will discuss the measures which should be undertaken in upcoming years in order to improve the results of surgery.

## Issues regarding the use of current definitions in liver surgery

### Metabolic syndrome

The definition of MS has evolved during the past decade. Current consensual criteria for its diagnosis include central obesity, hypertension, dyslipidemia (with either increased triglycerides level or decreased high density lipoprotein cholesterol level), and glucose intolerance.<sup>1</sup> The presence of at least three out of five of the abovementioned criteria are required to confirm the existence of MS.<sup>1</sup> Yet, liver histological manifestations and influence on surgical outcomes after liver surgery may occur in patients presenting with individual components of MS. Indeed, fatty liver disease may also occur in patients with isolated diabetes mellitus (DM),<sup>14</sup> hypertriglyceridemia,<sup>15</sup> and obesity.<sup>16,17</sup> Likewise, higher perioperative morbidity or mortality rates after liver resection have been reported in patients with only DM,<sup>18,19</sup> or who are overweight/obese,<sup>20,21</sup> or the association of several of these disorders.<sup>13,22</sup>

Interestingly, most surgical studies, because of their retrospective nature, do not 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<sup>8,11</sup> and that patients receiving antihypertensive therapy have hypertension. However, some of these medications may be used for primary cardiovascular prevention or renal protection in the absence of MS disorders.

In the same way, central obesity and visceral adiposity are often assessed using the body mass index. In this setting various cut-off values have been proposed.<sup>8,12,13</sup> Yet, BMI does not distinguish between central obesity, which is included in MS, from peripheral obesity. In that sense, circumference of waist appears to be more reliable and should be preferentially used.<sup>23,24</sup> Finally, the terms hyperglycemia and insulin-resistance are often used indiscriminately, whereas some authors suggest that they should not.<sup>1,25</sup> Hence, the presence of insulin-resistance should be routinely assessed using the homeostasis model assessment of insulin resistance (HOMA-IR)<sup>25</sup> whenever hyperglycemia is found.

### NAFLD

NAFLD has become one of the most frequent forms of chronic liver disease in Western countries.<sup>5,6</sup> The presence of NAFLD is defined by a fatty infiltration exceeding 5% of the liver parenchyma at histology in the absence of previous or ongoing significant alcohol consumption.<sup>26</sup> However, one should nevertheless bear in mind that a significant proportion of MS patients with fatty liver changes also have a history of daily alcohol consumption above 20–30 g per day and strict definition of NAFLD probably underestimates its true prevalence among MS patients. Although NAFLD is considered the hepatic manifestation of MS, other conditions including chronic hepatitis B and C infection,<sup>27,28</sup> irinotecan-based chemotherapy<sup>29,30</sup> and several other medications including methotrexate, tamoxifen or amiodarone<sup>31,32</sup> 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),<sup>26</sup> can progress to cirrhosis and may lead to end-stage liver disease.<sup>5,6</sup> Histological analysis remains the gold standard for the assessment of NAFLD and should be performed by a trained pathologist.<sup>33</sup> Several histological scores might be useful for the diagnosis of NAFLD. The most frequently used score is the non-alcoholic liver disease activity score (NAS) proposed by Kleiner et al,<sup>26</sup> which is a semiquantitative, histology-based score system including three parameters, namely steatosis (on a scale of 0 to 3), lobular inflammation and hepatocellular ballooning (on a scale of 0 to 2 each). More recently, Bedossa et al published a histopathological algorithm and scoring system for the evaluation of liver lesions in morbidly obese patients.<sup>34</sup> In this setting, the authors observed that this so called SAF score based on steatosis (S), activity (A) of the disease (ballooning and lobular inflammation) and fibrosis (F) grade in the underlying liver allowed decreasing interobserver varia-

tions among pathologists and was likely to be implemented in routine pathology practice.<sup>35</sup>

## NASH

NASH is considered the result of long-lasting inflammation following fatty liver infiltration. It is characterized by several histological alterations, including steatosis, lobular inflammation, and ballooning and may also be associated with fibrosis. Even though the diagnosis of NASH was initially suggested for NAS values of 4 or 5,<sup>26</sup> there is an ongoing debate regarding the accuracy of NAS in assessing NASH. Interestingly, Brunt et al have emphasized that the diagnosis of NASH based on the evaluation of patterns as well as individual lesions on liver biopsies did not always correlate with threshold values of the semiquantitative NAS.<sup>33</sup> Thus, rather than being based on the NAS value alone, the differentiation between NASH and no-NASH should better take into account the pathologist report.<sup>33</sup>

## Identification of NASH in patients with MS/NAFLD

Since the increasing incidence of both MS and NAFLD in Western populations put a great amount of patients at risk of developing NASH, any large-scale screening policy aimed to obtain histological diagnosis of NAFLD is unlikely to be reasonably performed. Furthermore, the accuracy of histology in identifying NASH is suboptimal as both interobserver variations<sup>36</sup> and discrepancies from one sample to the other within the same parenchyma may occur.<sup>37</sup> 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 (ALT/AST ratio; FIB-4; analysis of organic compounds in breath),<sup>38</sup> and imaging techniques (magnetic resonance imaging [MRI] for quantification of liver steatosis<sup>39</sup> or magnetic resonance spectroscopy) have been proposed for the detection of underlying parenchymal changes among patients with MS, but none has yet become the gold standard. In particular, although MRI has shown high accuracy in detecting steatosis, its effectiveness in evaluating (and possibly ruling out) fibrosis remains questionable in the presence of fat.<sup>40</sup>

## MS/NAFLD influence on primary liver carcinogenesis

Two recent series have shown that MS itself was associated with an increased risk of developing HCC.<sup>3,41</sup> In this setting, HCC incidence in patients with MS has been reported to be

2–4 fold higher than in the general population.<sup>7</sup> How MS acts to promote carcinogenesis remains to be fully elucidated. In this setting, liver tumorigenesis might be indeed complex, involving potential direct pro-tumoral actions of insulin-resistance<sup>42</sup> and obesity<sup>43</sup> but also indirect effects related to the development of underlying NAFLD.<sup>5,6</sup> On one hand, direct oncologic effects may be the consequence of low-grade, chronic systemic inflammation, implying a serum increase of inflammatory cytokines such as TNF- $\alpha$  and IL-6<sup>5</sup> and a decrease in anti-inflammatory ones including adipocytokines<sup>44</sup> potentially leading to loss of tumor suppression genes and deregulation of several signaling pathways such as the AMPK/mammalian target of rapamycin (mTOR) pathway.<sup>45</sup> This mechanism likely explains the absence of severe underlying fibrosis in as much as 30%–60% of the patients with MS-related HCC<sup>7,8,22,46</sup> including almost 20% of patients with a strictly normal underlying liver parenchyma. On the other hand, 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%<sup>5</sup> leading to a cumulative five-year incidence ranging from 7.6%<sup>47</sup> to 11%.<sup>48</sup> In the event of NASH-related cirrhosis, both the presence and pattern of hepatic iron deposition<sup>49,50</sup> as well as any regular alcohol consumption<sup>6</sup> have been incriminated to further accentuate parenchymal changes thus promoting liver carcinogenesis.

Finally, viral 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 mentioning. 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.<sup>27,28,51,52</sup> A significant number of the 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,<sup>53</sup> its existence has been incriminated in recurrence of HCV-related HCC<sup>54</sup> 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.

## MS/NAFLD impact on outcome of liver surgery

The impact of individual components of MS and liver steatosis on the postoperative course following liver resection has been extensively investigated.<sup>18,55-59</sup> Accordingly, it has been established that liver surgery provided poorer results in patients affected by diabetes<sup>18</sup> or obesity<sup>55,56</sup> than in otherwise healthy patients. Similarly, several studies have highlighted that steatosis per se was a risk factor for postoperative complications after major hepatectomy.<sup>57-60</sup> 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.<sup>61</sup> Nevertheless, it is only recently that surgeons have focused on the results of liver resection and transplantation, in the specific subset of patients with MS or NASH.

### Liver resection

Up to now, only six studies have analyzed the early outcome of patients undergoing liver resection in a setting of MS/NASH.<sup>8-13</sup> Of these, three aimed at assessing the influence of MS on outcome,<sup>8,12,13</sup> whereas the remaining three aimed at evaluating the impact of histological modifications, including NAFLD and NASH.<sup>9-11</sup> Overall, mortality after liver resection varied from 3% up to 30%, and was related to the primarily studied parameter ie, MS, NAFLD or NASH. In this setting, it has been recently suggested that MS patients with a NAS >2<sup>8</sup> or those with an histological diagnosis of NASH<sup>11</sup> had a 2.7-fold greater risk of experiencing liver-related but also cardiorespiratory complications than those with normal underlying parenchyma. Hence, it seems that steatohepatitis rather than simple steatosis was a risk factor for postoperative complications.<sup>11</sup> Even if these recent findings may appear in opposition with previously published results maintaining a negative impact of steatosis on outcome,<sup>58-60</sup> it is likely that the poor assessment of inflammatory changes in the underlying steatotic parenchyma may have biased older series. However, 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),<sup>13</sup> and trisectionectomy,<sup>10</sup> although a safe amount of liver parenchyma was left in place. This result clearly emphasizes the inferior 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.<sup>8,22</sup>

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 of the degree of visceral adiposity,<sup>62,63</sup> thus leading to higher incidence of cardiorespiratory events following liver resection. Possibly, the recently described hemorheological alterations occurring in MS patients, including increased erythrocyte aggregation,<sup>64,65</sup> may also play a role in ischemic cardiac events. Likewise, even though not documented, potential changes in coagulation in MS patients could influence the postoperative course of these patients. This is particularly true following major resection after which the normal coagulation profile is largely modified but also considering the pre-existing pro-thrombotic state in the absence of underlying cirrhosis leading to increased risk of pulmonary embolism.<sup>66</sup>

### Liver transplantation

NASH can progress to cirrhosis<sup>2,4</sup> 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 2000s up to 19% in 2011.<sup>2</sup> Currently, NASH is the third most common cause of LT in the US and is about to become the most common within the next two decades in Western countries.<sup>67</sup>

LT in NASH patients has peculiar aspects. Compared with other patients undergoing LT, recipients with NASH tend to be older<sup>68</sup> and obviously have a higher frequency of metabolic disorders.<sup>62</sup> In this setting, procedures significantly last longer and are associated with higher blood loss and longer post-transplantation hospital stays.<sup>62</sup> Accordingly, 30-day mortality after LT in patients with NASH tends to be higher than that for other indications.<sup>69</sup> Several studies have reported increased liver related morbidity rates in NASH patients, such as acute rejection rates<sup>68</sup> but also extra-hepatic complications, including sepsis and renal dysfunction.<sup>70</sup> Similarly to patients undergoing hepatectomy, NASH patients



undergoing LT also have a higher likelihood of developing cardiovascular complications.<sup>62,68,70</sup> 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.<sup>62</sup> 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 with MS whenever NASH is present.<sup>71</sup> In fact, similarly to what has been observed after liver resection (LR), NASH is nowadays thought to put patients at an even higher risk of cardiovascular complications, regardless of comorbidities and patient-specific cardiac risk.<sup>62</sup> 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 for NASH are encouraging. One-, 3- and 5-year survivals after LT for NASH range from 84%–87.6%, 75%–82.2%, and 70%–76.7%, respectively, and are at least similar to those observed for LT for other traditional indications.<sup>2,62,68,69,72</sup> More interestingly, LT for HCC developed in patients with NASH seems to provide an excellent long-term outcome with higher survivals compared with patients transplanted for HCV-related HCC.<sup>73</sup> These observations could be the result of less aggressive tumors in NASH patients with lower vascular invasion and decreased rates of poorly differentiated lesions.<sup>74</sup>

LT in patients with NASH-related cirrhosis presents peculiar issues, including cirrhosis. Recurrent disease after LT for NASH-related cirrhosis has been reported to occur in as high as 34% of recipients.<sup>69,75</sup> 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.<sup>76</sup> Nevertheless, in these patients, recurrence is often associated with the presence of MS or its individual components.<sup>75</sup> Accordingly, recurrence should be further evaluated in larger studies, with special emphasis on management of MS and secondary prevention strategies.<sup>75</sup>

## 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 inferior tolerance

to extended resection of fatty and inflammatory livers (as a consequence of lower regenerative ability), requires specific focus during 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 entered clinical practice even in specialized environments. Addressing this issue, our group has recently shown that MS patients operated on for HCC less frequently underwent preoperative portal vein embolization (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 from a better anticipation of their operative risk, especially in the case of planned major LR.<sup>8</sup>

In general, preventing measures to reduce MS/NAFLD-related morbidity/mortality should include: i) 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; ii) MS targeted perioperative management including complete perioperative cardiorespiratory work-up and monitoring as well as continuous postoperative blood glucose control;<sup>77,78</sup> and iii) specific, “NAFLD-tailored” perioperative 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.<sup>79</sup> 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.<sup>80</sup> 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.<sup>81–83</sup> More recently, retrospective studies have shown that the use of biguanides, such as metformin, was associated with a systematic HCC risk reduction among diabetic patients while this risk was not decreased using several other antidiabetic therapies.<sup>84,85</sup> While the precise antitumoral mechanisms of metformin in a setting of HCC still remain to be fully elucidated, there is growing evidence that LKB1-dependent and AMPK-dependent suppression of the mTOR pathway is possibly the most potent antineoplastic effect of metformin.<sup>86,87</sup> Indeed, mTOR inhibition disturbs protein synthesis and, thereby, tumor cell proliferation.<sup>87</sup> Hence, several therapies aiming at inhibiting the mTOR pathway have recently proved efficient in patients with various malignancies including breast cancer,<sup>88</sup> renal cell carcinoma<sup>89</sup> and pancreatic endocrine tumour.<sup>90</sup> Experimentally, metformin has recently shown promising results in the prevention of HCC development<sup>91</sup> but also in the limitation of tumor growth in rodents.<sup>92–95</sup> Altogether, in a context of MS/NAFLD related HCC, metformin would theoretically represent an ideal preventing therapy limiting the influence of type II diabetes in the occurrence of HCC 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 surgery. This consideration gains interest if one considers that the great majority of patients undergoing major liver surgery (LR and LT) present 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 conditions referred to hepatobiliary units is to be expected. The higher operative risk observed in these patients can be partially explained by both underestimated liver-related risk but also high perioperative cardiovascular and respiratory susceptibility. These unsatisfactory postoperative results will require targeted

perioperative management. Such actions are justified by the observed favorable long-term outcomes.

## Disclosure

The authors report no conflict of interest in this work.

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