RAPPORTI ISTISAN 25|28

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ITA-MASLD
(Italian observational study on Metabolic dysfunction-Associated Steatotic Liver Disease)

Clinical-epidemiological profile and management of patients with MASLD in multidisciplinary care setting in Italy

M.G. Quaranta, B. Mattioli, B. Buttari, L. Ferrigno, S. Rosato, L.A. Kondili
for the ITA-MASLD Executive Committee

EPIDEMIOLOGIA
E SANITÀ PUBBLICA

ISTITUTO SUPERIORE DI SANITÀ

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Maria Giovanna Quaranta (a), Benedetta Mattioli (a), Brigitta Buttari (b), Luigina Ferrigno (a), Stefano Rosato (a), Loreta A. Kondili (a) for the ITA-MASLD Executive Committee

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2025, iii, 48 p. Rapporti ISTISAN 25/28

The ITA-MASLD cohort study is a multicentre observational study aimed at characterizing the clinical and epidemiological profile of patients with MASLD and liver fibrosis, managed in multidisciplinary care centres across Italy. It also evaluates the impact of integrated care pathways on healthcare outcomes and associated economic costs. Combining prospective and retrospective data, the study gathers information from medical records, outpatient evaluations, diagnostic reports, and patient-reported outcomes. Key objectives include analysing comorbidities, treatment patterns, resource utilization, and patients' quality of life. Ethical compliance, data protection, and informed consent are ensured. Findings are expected to inform health policies and support more effective, patient-centred organizational models for MASLD management.
Key words: Metabolic dysfunction-associated steatotic liver disease; Real-word evidence; Health policy; Multidisciplinary study; Cohort study

Istituto Superiore di Sanità
ITA-MASLD (Studio osservazionale italiano sulla malattia epatica steatosica associata a disfunzione metabolica). Profilo clinico-epidemiologico e gestione dei pazienti con MASLD in contesti di assistenza multidisciplinare in Italia.
Maria Giovanna Quaranta, Benedetta Mattioli, Brigitta Buttari, Luigina Ferrigno, Stefano Rosato, Loreta A. Kondili per il Comitato Esecutivo ITA-MASLD
2025, iii, 48 p. Rapporti ISTISAN 25/28 (in inglese)

Lo studio osservazionale ITA-MASLD è uno studio multicentrico volto a caratterizzare il profilo clinico-epidemiologico dei pazienti affetti da MASLD (malattia epatica steatosica associata a disfunzione metabolica) e fibrosi epatica, seguiti in centri di cura multidisciplinari in Italia. Lo studio valuta anche l'impatto dei percorsi assistenziali integrati sugli esiti clinici e sui costi sanitari. Attraverso una raccolta di dati sia retrospettiva che prospettica, vengono analizzate informazioni da cartelle cliniche, visite ambulatoriali, referti diagnostici e questionari validati compilati dai pazienti. Gli obiettivi principali includono l'analisi delle comorbidità, dei percorsi di cura, dell'utilizzo delle risorse e della qualità della vita. Il protocollo garantisce il rispetto delle normative etiche, la protezione dei dati e il consenso informato. I risultati attesi forniranno indicazioni utili per le politiche sanitarie e per lo sviluppo di modelli organizzativi più efficaci e centrati sul paziente nella gestione della MASLD.
Parole chiave: Steatosi epatica associata a disfunzione metabolica; Evidenze real-word; Politiche sanitarie; Studio multidisciplinare; Studio osservazionale di coorte

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METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: AN INTRODUCTION

The National Centre for Global Health at the Istituto Superiore di Sanità (ISS, the National Institute of Public Italy Health in Italy), building on its long-standing experience in the surveillance of chronic liver diseases and the success of the Italian platform for the study of viral hepatitis therapies (PITER, *Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali*) (1), has promoted and coordinated the design of the ITA-MASLD observational study, the first nationwide, multicenter, prospective observational study on Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) in Italy, conducted in collaboration with the Department of Cardiovascular, Endocrine-Metabolic Diseases and Aging, which contributes its expertise in metabolic disorders, cardiovascular risk, and age-related comorbidities to ensure a comprehensive characterization of MASLD patients.

MASLD is a largely silent but rapidly growing public health threat. Strongly associated with type 2 diabetes, obesity, and metabolic syndrome, MASLD can evolve into cirrhosis and hepatocellular carcinoma (HCC) if left undiagnosed or inadequately managed.

This national initiative is aimed at generating real-world evidence on the clinical, epidemiological, and economic burden of MASLD in Italy. The study is built upon the operational model of PITER and benefits from its extensive network of clinical centres distributed across the country (1). For the ITA-MASLD project, the PITER network has been expanded to include additional specialized clinical centres, thus establishing a dedicated national platform for MASLD. Recognizing MASLD as a systemic condition that transcends hepatology, the project builds on a unique national alliance of scientific societies spanning hepatology, diabetology, internal medicine, gastroenterology, and obesity. This collaborative model ensures that clinical diversity is reflected in study design, patient recruitment, and future implementation pathways.

The initiative is conducted under the scientific oversight of the Italian Association for the Study of the Liver (AISF, Associazione Italiana Studio del Fegato) and benefits from the strategic collaboration of a broad multidisciplinary alliance comprising key scientific societies involved in the management of MASLD: the Italian Society of Diabetology (SID, Società Italiana di Diabetologia), the Italian Society of Gastroenterology and Digestive Endoscopy (SIGE, Società Italiana di Gastroenterologia ed Endoscopia digestiva), the Italian Society of Internal Medicine (SIMI, Società Italiana di Medicina Interna), the Italian Society of Obesity (SIO, Società Italiana dell'Obesità), the Club of Hospital Hepatologists (CLEO, Club Epatologi Ospedalieri), and the Italian Association of Hospital Gastroenterologists (AIGO, Associazione Italiana Gastroenterologi Ospedalieri).

The multidisciplinary approach enables comprehensive and integrated patient management through the synergistic collaboration of hepatologists, internists, diabetologists, infectious disease specialists, and obesity experts, enabling a comprehensive and integrated approach to patient management. The network plays a pivotal role in identifying, enrolling, and monitoring patients with MASLD and liver fibrosis, ensuring harmonized data collection across both cross-sectional and prospective dimensions. This coordinated infrastructure facilitates the generation of robust real-world evidence and fosters inter-institutional scientific collaboration, thereby enhancing the study's potential to inform clinical practice and guide public health strategies.

The ITA-MASLD study aims to establish a representative cohort of patients with documented MASLD, including patients with alcohol consumption defined as MetALD (metabolic dysfunction–associated alcohol-related liver disease) currently receiving specialist care, with the objective of characterizing disease progression, comorbidity profiles, and healthcare resource

utilization, laying the foundation for data-driven and equitable health policy planning. In addition, the study incorporates a Cost Of Illness (COI) component aimed at quantifying not only the current economic burden of MASLD, but also the projected costs of inaction, that is, the healthcare and societal consequences of failing to implement early detection and intervention strategies.

This innovative approach, which combines clinical, economic, and system-level perspectives, positions ITA-MASLD as a critical tool to support more equitable, sustainable, and effective public health policies in response to the growing burden of MASLD.

Clinical and economic impact of MASLD

MASLD is a chronic liver condition characterized by the accumulation of excess fat in the liver (hepatic steatosis) in individuals with at least one cardiometabolic risk factor, such as obesity, type 2 diabetes, hypertension, or dyslipidaemia (2). MASLD represents the hepatic manifestation of systemic metabolic dysfunction and encompasses a spectrum of disease severity. In its earliest stage, MASLD is defined by steatosis without significant inflammation or hepatocellular injury. This form is typically asymptomatic and often detected incidentally through imaging or detection of persistently elevated liver enzymes. The natural history of MASLD is characterized by a slow and heterogeneous progression, strongly influenced by individual metabolic, genetic, and environmental factors. MASLD initially manifests as simple hepatic steatosis, which is often asymptomatic and reversible with lifestyle modifications. In MASLD, hepatocytes store triglycerides in large lipid droplets, leading to macrovesicular steatosis, which involves more than 5% of hepatocytes. At this stage, there is no or minimal hepatocellular ballooning, lobular inflammation, or fibrosis.

However, a subset of patients progresses to Metabolic Dysfunction-Associated Steatohepatitis (MASH) which involves fat accumulation leading to lipotoxicity, inflammation, and hepatocyte damage (3). MASH is characterized by lobular inflammation and hepatocyte swelling and carries a higher risk of fibrosis and progression. Fibrosis is the primary determinant of long-term outcomes, and its progression can vary widely, from minimal changes over decades to rapid advancement to cirrhosis within a few years in high-risk individuals (Figure 1).

Factors associated with accelerated disease progression include older age, type 2 diabetes, obesity, alcohol use, and specific genetic polymorphisms (e.g., *PNPLA3* and *TM6SF2*). The presence of metabolic syndrome (obesity, dyslipidaemia, hypertension, diabetes, or glucose intolerance) increases the risk of MASH compared to simple steatosis (4). While the average annual fibrosis progression rate is estimated at approximately one stage per 7-10 years in MASLD, this rate may be significantly faster in patients with MASH. Advanced fibrosis (F3-F4) is associated with increased risks of liver-related complications, including cirrhosis, HCC, and liver failure, as well as heightened cardiovascular morbidity and mortality, making early identification and risk stratification essential. Importantly, steatosis is considered reversible, particularly with lifestyle changes such as weight loss (≥5–10 %), improved glycaemic control, and regular physical activity (5,6). MASH typically affects individuals aged 40-60 but can occur at any age. The diagnosis of MASLD requires evidence of hepatic steatosis through imaging or liver histology, combined with at least one metabolic risk factor and no significant alcohol consumption (2).

According to the recent European Association for the Study of the Liver-European Association for the Study of Diabetes-European Association for the Study of Obesity (EASL-EASD-EASO) guidelines (7), screening for MASLD with liver fibrosis is recommended even in individuals with cardiometabolic risk factors or abnormal liver enzymes, regardless of a diagnosis of hepatic steatosis.

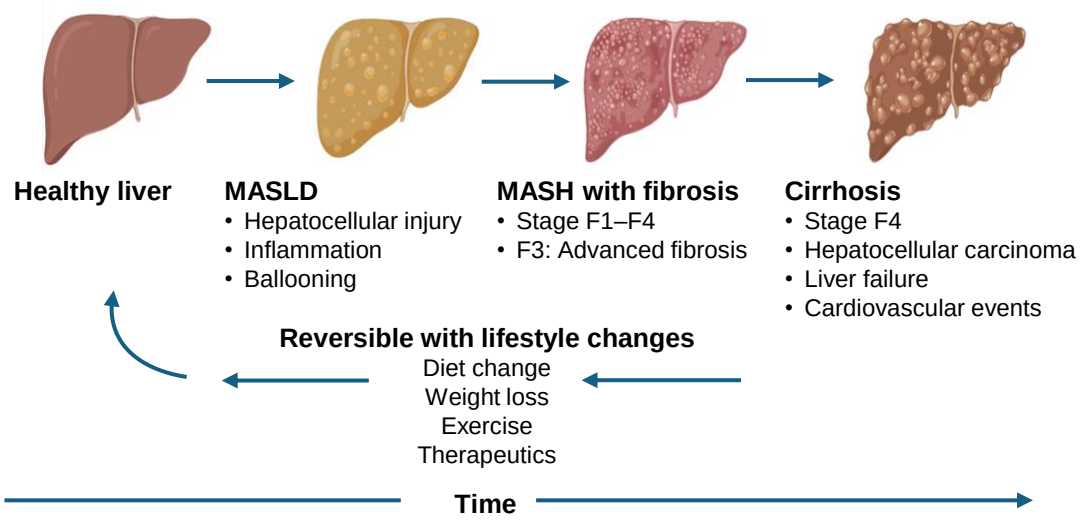

Figure 1. Natural history and rate of progression of MASLD

MASLD displays sexual dimorphism (8), with higher prevalence in men. However, after menopause the incidence in women increase, suggesting a protective role of oestrogen (9). In adolescents, MASLD is more frequent in females, likely due to differences in adipose tissue distribution and adipocytokine profiles (10). Nevertheless, despite the lower prevalence in adolescent males, they tend to exhibit more adverse metabolic features and greater visceral adiposity (10). MASH, however, is more severe in men, who are at a greater risk for fibrosis and hepatocellular carcinoma (8). The biological basis for these sex differences is unclear, as most preclinical studies focus on male animals, highlighting the need for more inclusive research. MASLD progression is driven by mechanisms like hepatic steatosis, mitochondrial dysfunction, oxidative stress, and chronic inflammation, with fibrosis being the principal driver of liver-related mortality (11).

MASLD is estimated to affect approximately 30% of the adult population worldwide, with its prevalence rising from 22% to 37% between 1991 and 2019 (12–14). This increase parallels the growing prevalence of obesity and related metabolic conditions, confirming a strong association between MASLD prevalence and key metabolic risk factors. Notably, the prevalence is significantly higher among individuals with type 2 diabetes (70.2%) and those who are overweight or obese (70.7%) (15–17).

A modelling study by Estes *et al.* projected a substantial increase in the prevalence and disease burden of MASLD across China, France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States between 2016 and 2030 (18). The model predicts a marked rise in MASLD cases driven by the increasing prevalence of obesity and type 2 diabetes. This upward trend is expected to result in a corresponding increase in advanced liver disease, including MASH, cirrhosis, and liver-related mortality, underscoring the urgent need for effective public health interventions to address the global MASLD epidemic.

MASLD is emerging as one of the leading causes of liver-related morbidity and mortality, HCC, and liver transplantation worldwide. Severe liver fibrosis significantly increases mortality risk, which escalates as fibrosis progresses. Beyond its direct health impacts, MASLD contributes to reduced quality of life, leading to mental health challenges, and increased healthcare resource utilization, including higher rates of emergency care visits and hospitalizations (19,20). The

economic burden is significant, with annual costs in Europe estimated at €35 billion in medical expenses and €191 billion in social costs (21–25). MASLD is also a major contributor to systemic complications, including cardiovascular diseases and extrahepatic cancers (21,24,26). With rising prevalence and associated costs, addressing MASLD through effective prevention, early diagnosis, and management strategies is critical to reducing its global impact.

In Italy, the prevalence of MASLD is estimated to affect over 25% of the adult population in line with European averages, with even higher rates observed in individuals with metabolic comorbidities such as obesity and type 2 diabetes (21,27). The clinical and economic burden is substantial, with increasing numbers of patients progressing to advanced fibrosis and cirrhosis, contributing to the growing demand for liver transplantation. Regional disparities in awareness, screening, and access to hepatology care, further complicate disease management. National strategies to standardize diagnostic pathways and integrate MASLD care into chronic disease networks are urgently needed to mitigate its impact.

Lifestyle intervention and advancing pharmacological options for MASLD

Lifestyle intervention remains the cornerstone of MASLD management, particularly in its early stages and in patients with liver fibrosis. Evidence consistently supports that modest weight loss (≥7-10% of body weight) through caloric restriction and regular physical activity improves steatosis, inflammation, and fibrosis. Structured lifestyle programs targeting dietary quality, physical fitness, and alcohol cessation are critical in modifying disease trajectory and reducing metabolic risk factors. Diet and physical activity can even reverse advanced fibrosis up to the stage of cirrhosis (28,29). Although cirrhosis itself is typically not reversible with diet alone, dietary interventions remain crucial for disease management and reducing hepatocellular carcinoma risk.

Figure 2 summarizes genetic susceptibility and modifiable risk factors in MASLD, emphasizing that healthy lifestyle behaviours remain the cornerstone of both primary and secondary prevention and overall disease management.

Despite the efficacy of lifestyle changes, adherence remains suboptimal in clinical practice, underscoring the need for additional therapeutic strategies. In this context, several pharmacological agents are currently in advanced phases of development, aiming to target key pathophysiological mechanisms such as insulin resistance, inflammation, oxidative stress, and fibrogenesis. Resmetirom, a thyroid hormone receptor-β agonist, is the only FDA-approved drug for MASH with advanced fibrosis, while other promising treatments targeting fibrosis are under investigation (30). Among emerging therapies, Glucagon-Like Peptide-1 (GLP-1) receptor agonists such as semaglutide have shown significant benefits in reducing liver fat and improving metabolic parameters, with potential antifibrotic effects (31–33). Additional agents include Farnesoid X Receptor (FXR) agonists (e.g., obeticholic acid), Peroxisome Proliferator-Activated Receptor (PPAR) agonists (e.g., lanifibranor) (34–36) and dual or pan-receptor modulators (e.g., tirzepatide, combining Glucose-Dependent Insulinotropic Polypeptide (GIP)/GLP-1, have shown histologic improvements in MASH and fibrosis (37–39), offering promising avenues for patients with progressive disease and representing a significant advancement in the therapeutic landscape of MASLD.

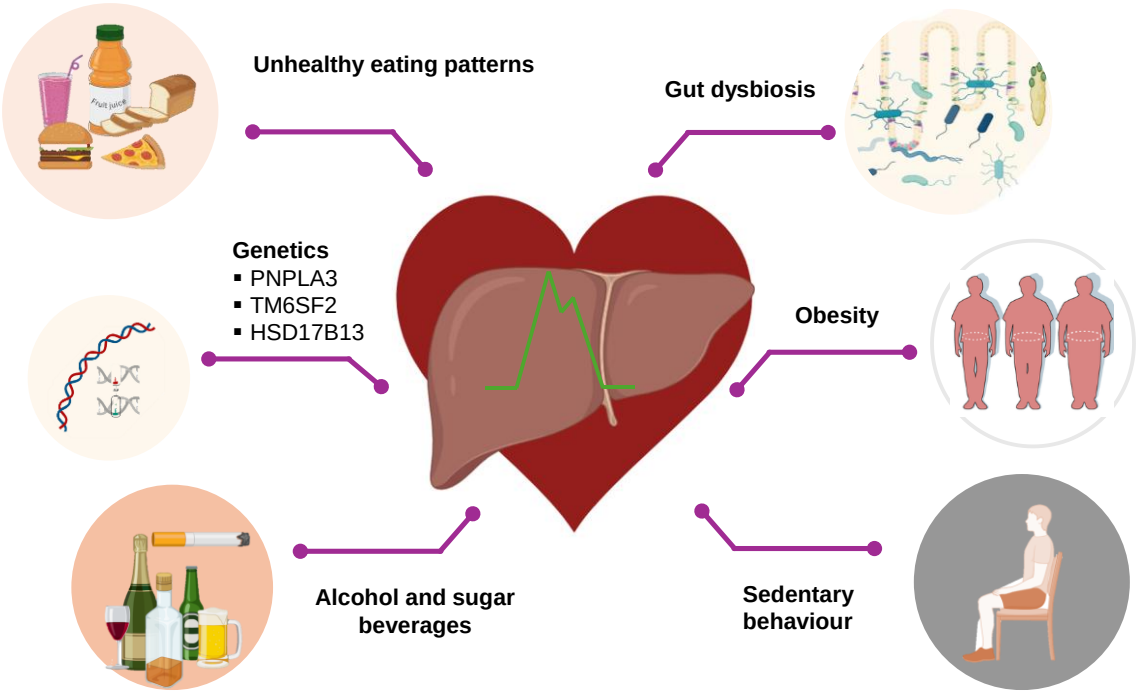

Figure 2. Genetic susceptibility and modifiable risk factors in MASLD

ITA-MASLD COHORT STUDY

The ITA-MASLD, based on a large prospective cohort of patients managed in real-life clinical settings, represents an innovative and strategic effort to validate and extend findings from controlled clinical studies on MASLD within the broader population. Its primary aim is to assess long-term outcomes, including disease progression, and healthcare utilization, across diverse patient categories, many of whom are underrepresented or excluded from regulatory trials. This real-world evidence will be essential for guiding the appropriate and efficient use of emerging MASLD therapies, allowing the National Health Service to prioritize interventions based on clinical severity, comorbid conditions, and social vulnerability.

The study targets the enrolment of several thousand individuals and includes both patients with confirmed MASLD (including those classified as MetALD) and liver fibrosis currently under care, as well as those not yet undergoing treatment, but who may become candidates for future pharmacological intervention. This cohort will serve as a dynamic and evolving national database, forming the backbone for future clinical research and observational spin-off studies.

Study design

ITA-MASLD is a prospective, multicentre, observational cohort study involving adult patients with MASLD (including those classified as MetALD) and liver fibrosis, who are receiving care in hepatology, internal medicine, diabetology, and related specialties across Italy.

The first version of the study protocol design was finalized in October 2024 and subsequently implemented in December 2024 for the collection of SDOH, as described below, while sites were selected and involved. The study received ethical approval and started enrolment from December 2024. The study will span 15 years, consisting of a 5-year enrolment period (from December 2024 to December 2029) followed by a 10-year prospective follow-up (until approximately December 2039, based on the date of the last enrolment). Figure 3 illustrates the timeline of the study.

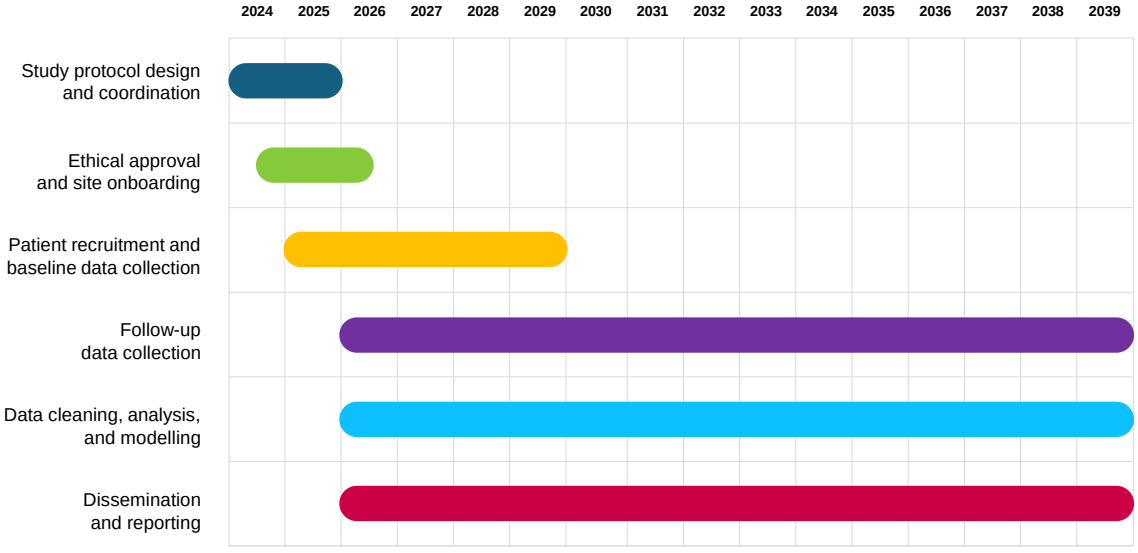

Figure 3. Project timeline of the ITA-MASLD Study

Patient enrolment and selection of clinical centres

All clinical centres with a multidisciplinary profile involved in the PITER network are invited to participate in the ITA-MASLD study. To ensure a multidisciplinary approach essential for managing MASLD and related comorbidities, each of the Governing board of the Scientific Societies that collaborate into the study will invite clinical centres with multidisciplinary profile or select representative clinical centres.

In addition, any clinical centre with multidisciplinary profile that is willing to participate in the study can join by directly contacting the study coordination team at ISS. Expressions of interest can be submitted via email to masld@iss.it or through the dedicated link available in the public area of the IT platform: www.masld.it.

To approve the inclusion of an interested clinical centre, a preliminary questionnaire will be required to assess the following criteria:

- Availability of accredited laboratory facilities capable of conducting routine biochemical and diagnostic evaluations, as well as having a structured framework for liver disease assessment;
- The estimated number of MASLD patients with liver fibrosis managed over the past year;
- The centre's ability to collect and input clinical data into a standardized electronic Case Report Form (eCRF) throughout a follow-up period of at least 10 years.

Upon approval, participating centres will receive full access to the secure data entry platform and associated materials in compliance with privacy and data protection regulations.

Participating centres in the ITA-MASLD study will recruit patients based on standardized inclusion and exclusion criteria. Enrolment will occur during designated six-month windows to maintain consistency across sites.

Each centre's recruitment volume will reflect its patient base and operational capacity, ensuring balanced participation and the formation of a representative, methodologically sound cohort.

Centres able to continue with long-term monitoring may join the follow-up phase, which involves completing an annual follow-up form for each enrolled patient for up to 10 years. This flexible model supports ongoing data collection while accommodating the organizational realities of participating institutions.

Eligibility criteria

Eligible participants include individuals diagnosed with MASLD and liver fibrosis markers according to the latest diagnostic criteria (2). Patients will be consecutively enrolled during predefined enrolment windows, each lasting three consecutive months and occurring twice a year. These windows may vary seasonally in subsequent years. As an observational study, no specific treatments are mandated; clinical management remains at the discretion of the attending physicians or trainees at the respective centres.

An annual cross-sectional analysis will be performed to generate updated clinical-epidemiological snapshots throughout the 5-year enrolment period. The subsequent 10-year follow-up phase, contingent on feasibility assessments from the first year, will collect annual data on patient management and outcomes. This long-term phase aims to evaluate the disease's clinical and economic burden and the cost-effectiveness of therapeutic approaches, enabling a comprehensive understanding of disease progression and treatment impact over time.

Figure 4 illustrates the clinical eligibility assessment algorithm.

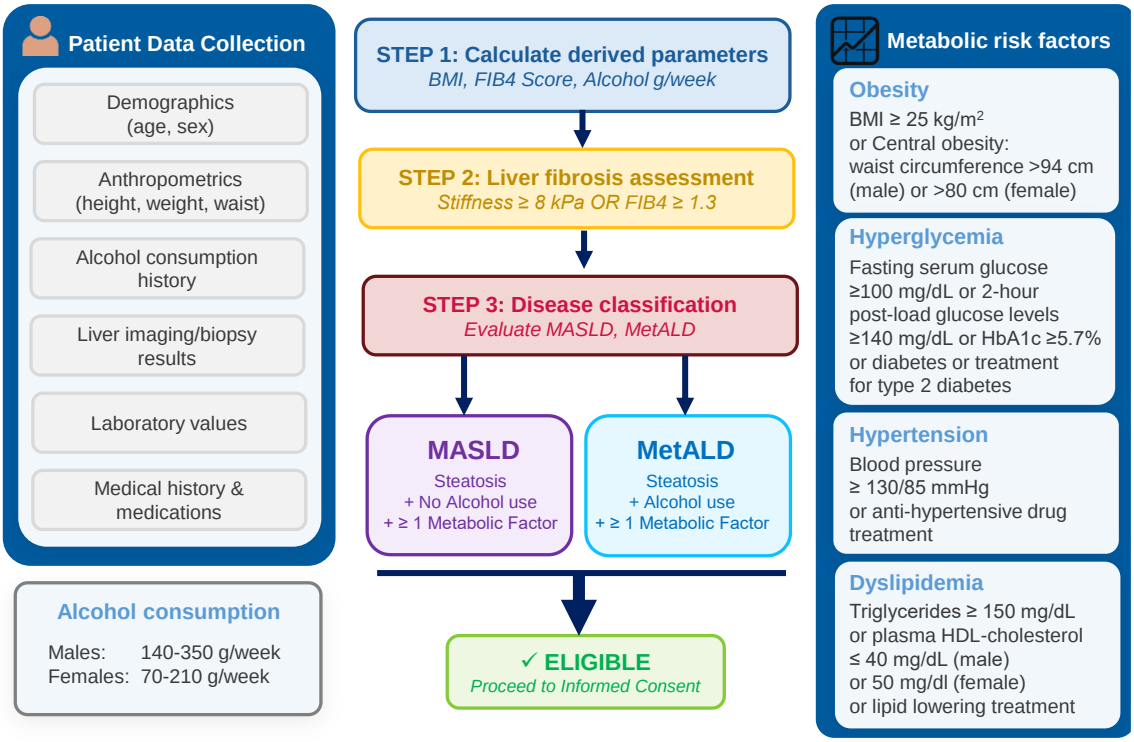

Figure 4. ITA-MASLD Study: specific algorithm to verify eligibility criteria

Inclusion criteria

The inclusion criteria of the study are here listed:

– Age ≥18 years;
– Individuals diagnosed with MASLD or MetALD with evidence of liver fibrosis, defined as liver stiffness measurement ≥ 8 kPa or Fibrosis-4 index (FIB-4) ≥ 1.3;
– Currently under follow-up at a participating clinical centre.

Eligible patients may include:

– Individuals in any clinical and histopathological state of liver disease;
– Individuals with history of chronic HCV infection with sustained virologic response (HCV RNA negative);
– Individuals with Chronic HBV infection under stable antiviral treatment;
– Individuals with HIV infection under effective antiretroviral therapy.

Exclusion criteria

The exclusion criteria of the study are here listed:

– Age under 18 years;
– Patients included in clinical trials (limited to the trial participation duration);

- Alcohol consumption >210 g/week for females and >350 g/week for males;
- Patients with active HCV infection;
- Patients with active chronic HBV infection not on therapy;
- Patients with Hepatitis D Virus (HDV) infection;
- Patients with untreated HIV infection;
- Patients with autoimmune hepatitis;
- Patients with liver damage from another defined aetiology (e.g., primary biliary cholangitis, Wilson's disease).

Main objectives

The ITA-MASLD study has been designed with the following main objectives, aimed at providing a comprehensive real-world assessment of MASLD and with the overarching goal of supporting evidence-based clinical practice, healthcare planning, and health policy decision-making in Italy:

- to characterize the clinical, metabolic and epidemiological profile of MASLD patients;
- to collect real-world data on patients with MASLD across different healthcare settings nationwide, describing their demographic, clinical, and socio-economic characteristics, comorbidity patterns, and disease severity;
- to assess the clinical and economic burden of MASLD to support evidence-based health policy;
- to estimate the impact of MASLD in terms of healthcare utilization, clinical outcomes, complications, and both direct and indirect costs. This includes generating evidence to support the design of cost-effective and patient-centred strategies for MASLD management.

Main expected results

The ITA-MASLD study is expected to generate a robust set of outcomes that will inform clinical practice, public health strategy, and healthcare planning in Italy:

- updated national estimates on disease burden, severity, comorbidities, and real-life patterns of diagnosis and management;
- identification of unmet clinical needs and care pathway variations across geographic areas and clinical specialities;
- evaluation of the adoption and effectiveness of multidisciplinary care models in MASLD management;
- assessment of the efficacy of lifestyle interventions and emerging pharmacological treatments in terms of clinical outcome, including disease progression, survival, and liver-related events. as well as surrogate endpoints;
- identification of predictors of disease progression and treatment response based on real-world evidence;

- analysis of regional and gender disparities in access to diagnostics and specialized care;
- longitudinal data collection on liver fibrosis progression and MASLD-related complications (e.g., cardiovascular events, hepatocellular carcinoma);
- monitoring of clinical outcomes, including hospitalization rates, liver-related events, and quality of life over time;
- evaluation of the impact of social determinants of health on disease progression and access to care;
- identification of high-risk and underserved groups to guide equitable interventions;
- estimation of healthcare resource utilization and cost-effectiveness of current MASLD screening and treatment strategies;
- development of evidence-based, personalized care algorithms to guide rational and equitable resource allocation;
- implementation of a COI model to define the economic burden of MASLD and project the avoidable costs related to inaction.

Governance

The governance of the MASLD cohort study is structured to ensure scientific rigor, transparency, and promote effective coordination among all participating institutions. Led by the ISS, the study is conducted in collaboration with a multidisciplinary Executive Committee that includes representatives from leading scientific societies (AISF, SIMI, SIO, SID, SIGE, CLEO, and AIGO) as well as patient advocacy groups. This committee oversees the study's strategic direction, ensures compliance with ethical and regulatory standards, and evaluates proposals for ancillary studies.

Clinical centres participating in the cohort follow a harmonized protocol for patient enrolment and data collection, supported by a centralized IT platform designed to ensure data security and pseudonymization. Regular communication and training activities promote quality control and foster alignment across all sites. This governance model facilitates collaborative decision-making, enhances data comparability between centres, and ensures that the study's outcomes are meaningful for clinical practice, health policy, and future MASLD research initiatives.

The establishment of a Scientific Committee, composed of the principal investigators from the most representative clinical centres, is planned.

Ethical aspects and protocol approval

The ethical governance of the ITA-MASLD has been meticulously structured to ensure full compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and both national and international regulations on the protection of human subjects and personal data.

The study protocol received formal approval from the National Ethics Committee of the ISS on December 12th, 2024. In line with Article 6, paragraph 2 of the Ministerial Decree (30/11/2021), each participating clinical centre is required to notify its local Ethics Committee, unless a formal opinion is explicitly requested by the Committee itself. Participation is voluntary and based on the informed consent of all patients prior to enrolment. All study activities will be conducted in accordance with the relevant ethical authorizations.

A multi-tiered approach was adopted for the approval process:

– national-level approval of the study protocol and patient informed consent form by the ISS Ethics Committee;
– local-level notifications or approvals by Ethics Committees of the participating centres, in accordance with specific institutional and regional procedures;
– review by the ISS-based coordination team of any feedback or specific requests from local committees.

In parallel with the ethical approval process, a formal collaboration agreement will be signed between the promotor (ISS) and each participating centre. This agreement will define roles, responsibilities, data management procedures, and the terms of participation, ensuring consistency, accountability, and adherence to the study protocol across all sites.

The ISS Ethics Committee's decision was formally documented and shared with all participating ITA-MASLD centres. Clinical Centres are involved in the study on voluntary basis. Each private financial support has been/will be evaluated by the National Ethic Committee of the ISS, according to strict conflict-of-interest policies, to ensure study impartiality and integrity. Future public and/or private funds will be required to support the study coordination and conduction.

As schematically represented in Figure 5, it is possible to propose:

– *Top-down studies*: initiated by the Executive Committee based on shared priorities.
– *Bottom-up sub-studies*: proposed by researchers from the ITA-MASLD network or external collaborators, subject to scientific and ethical approval.

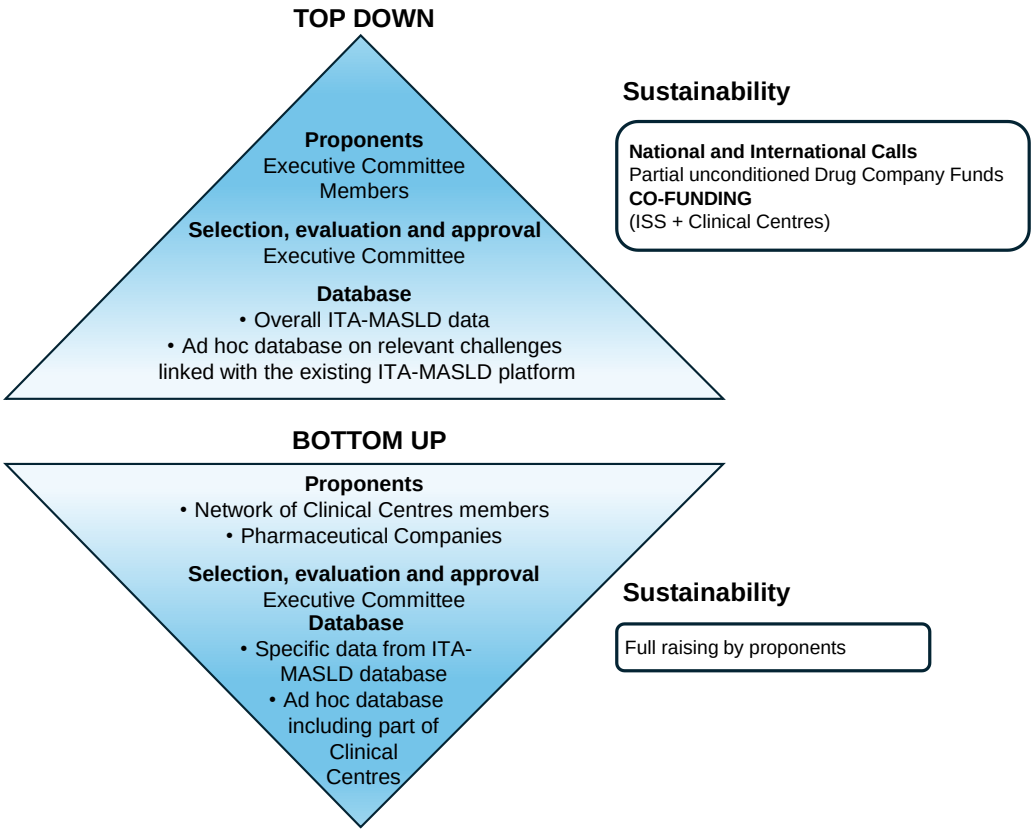

Figure 5. Representation of the evaluation process for top-down and bottom-up study proposals within the ITA-MASLD framework

Proposal submission process

Proposals must be submitted using a Research Proposal Summary Form.
The form must include the following information:

- Study title
- Name, affiliation, and contact details of the proposer
- Brief background (max 3 lines)
- Objectives
- Target population
- Methods and study design
- Estimated sample size
- Statistical analysis (centralized or independent)
- Expected timeline (analysis, first draft)
- Budget and resources
- Up to 3 bibliographic references
- Date of submission.

The proposal should be sent to the study ISS-based coordination team at the following email address: masld@iss.it

Proposal evaluation

The evaluation process consists of two phases:

- *Phase 1 – Technical assessment*
  Conducted by the Data Managers, who verify:
  - Alignment with the objectives of the protocol approved by the CEN
  - Availability of the required data in the cohort
  - Operational and numerical feasibility
  - Type and duration of the analysis
  - Feasibility of data extraction
- *Phase 2 – Scientific review*
  Conducted by the study ISS-based coordination team, based on the following criteria:
  - Absence of overlap with other approved studies
  - Scientific relevance and originality
  - Methodological and statistical soundness
  - Consistency with ITA-MASLD research priorities

All members involved in the evaluation process are bound by strict confidentiality.

Authorship criteria

The ISS-based coordination team promotes a transparent and inclusive authorship policy. Authorship for publications based on ITA-MASLD cohort data will be agreed upon at the time of sub-study approval and will be based on the following criteria:

- Quantity and quality of data provided by the centre;
- Substantial scientific contribution to the study design, data analysis, or interpretation;
- Active involvement in drafting or critically revising the manuscript;
- Participation in the final approval of the version to be published.

Data Managers and Executive Committee members may be listed as co-authors if they have made a substantial contribution, in line with ICMJE (International Committee of Medical Journal Editors) international criteria.

All sub-studies must aim to generate clinical evidence that is valuable for public health. The study coordination team is committed to supporting the most relevant initiatives and to fostering a collaborative and multidisciplinary environment.

ITA-MASLD PLATFORM: DEFINITION OF THE OPERATIVE PROCEDURE

The ITA-MASLD study protocol outlines the study's objectives, inclusion and exclusion criteria, and expected duration of follow-up. Data collected throughout the study include comprehensive clinical, laboratory, sociodemographic, and, when available, histopathological information. These data will be recorded in standardized eCRFs at the time of patient enrolment and during annual follow-up evaluations (Appendix A).

Special attention is given to the documentation of comorbidities and concomitant medications that may influence disease progression or management strategies, including cardiovascular disease, diabetes, obesity, and chronic or treated viral infections (HIV, HBV, and HCV with sustained virologic response). ITA-MASLD is a non-interventional observational study based solely on real-life data collected after obtaining informed consent. Specialists are responsible for clinical decisions, including pharmacological treatments, according to good clinical practice and current national and international guidelines.

Participation in the study does not influence treatment strategies, and refusal to participate does not impact care.

The study protocol details the following key procedures:

– verifying eligibility, obtaining informed consent, and labelling patient files with a study-specific identifier;

– specifying timing and methods for eCRF completion.

All clinicians must follow the procedural guide to ensure consistency, ethical compliance, and data quality.

ITA-MASLD web-based platform and eCRF

The ITA-MASLD study has implemented a dedicated, web-based platform to ensure efficient, secure, and standardized data collection across all participating clinical centres. The platform, developed specifically for the study, adheres to international data protection and quality standards, including ISO 27001 and General Data Protection Regulation (GDPR) compliance, and allows for real-time interaction among multidisciplinary teams involved in MASLD patient care and research.

This system is designed to be user-friendly, interoperable, and adaptable, enabling seamless data entry, secure sharing of information, and the integration of spin-off research studies using shared informatics infrastructure. The core data set is flexible enough to accommodate future modules for ancillary projects within the ITA-MASLD framework.

The eCRFs are specifically designed to reflect real-world outpatient clinical documentation. Their development involved close collaboration with the Executive Committee, which includes representatives from AISF focused on dysmetabolic associated liver disease, delegates from scientific societies engaged in the multidisciplinary management of MASLD, and clinical experts with long-standing collaboration with the Centre for Global Health of ISS in the field of liver diseases. Each form was thoroughly reviewed and approved by all members of the Executive Committee to ensure the collection of essential clinical data while minimizing any disruption to routine clinical workflows.

Overview of data entry procedures

This section provides step-by-step instructions for accessing the ITA-MASLD electronic data collection platform, entering and updating patient records, monitoring the status of data entries, and understanding the flow and validation of data, including saving procedures.

Access and authentication

Authorized users from participating clinical centres can access the ITA-MASLD data platform via personal credentials issued to the centre's designated investigator.

Upon logging in, users will be directed to a dedicated form designed to verify whether the patient meets the inclusion criteria. A specific algorithm has been developed to ensure full compliance with eligibility requirements and the proper acquisition of informed consent (*see* Figure 4).

Informed consent must be obtained and documented prior to entering any data in the enrolment eCRF.

The system will generate a unique pseudonymized patient ID derived from the individual's Italian tax code; however, the Italian tax code itself will not be stored.

This mechanism enables multidisciplinary input from different specialists managing the same patient at the centre, while preventing duplicate entries and overlaps, as each patient can only be registered once within the platform.

This approach ensures accurate labelling of patient records with a study-specific identifier, preserving both traceability and compliance with data protection standards.

Data entry

Data collected by the specialist physician during the enrolment visit, performed according to routine clinical practice and documented in the medical record, will be entered into the electronic case report forms (eCRFs) through structured input modules covering demographic, clinical, lifestyle, and disease-specific information, as outlined below.

eCRFs can be completed during or shortly after outpatient or inpatient visits. Clinical and laboratory data are recorded with corresponding dates. Once the enrolment eCRF is completed, follow-up CRFs are automatically activated, supporting seamless longitudinal tracking and data traceability. The platform generates interconnected datasets, linking patient records over time for comprehensive data integration.

This structured framework underpins national-level epidemiological monitoring, healthcare planning, and clinical research on MASLD.

Each patient is entered once. Additional data from subsequent visits or other specialists at the same centre will be merged under the same record.

Enrolment

Users will be guided through structured input modules (enrollment eCRF) including demographic, clinical, lifestyle, and disease-specific information, as outlined below.

– *Demographic, anthropometric, and social data*
  age, sex, Body Mass index (BMI) (calculated), and social determinants of health.

– *Social determinants of health*
environmental, behavioural, social and economic e.g., education, occupation, housing, income, access to care.

– *Detailed patient-reported and lifestyle data (in selected centres)*
alcohol, smoking, drug use, physical activity, and quality of life.

– *Metabolic profile and comorbidities*
presence of diabetes, cardiovascular disease, cancers, and other relevant conditions.

– *Liver disease-related data*

- Steatosis grade: assessed by ultrasound, Controlled Attenuation Parameter (CAP) and magnetic resonance imaging (MRI), or histology
- Fibrosis stage: based on transient elastography, MR elastography, non-invasive scores (e.g., FIB-4, NFS), or histology
- Advanced liver disease: presence of HCC and/or decompensation (ascites, portal hypertension, varices, encephalopathy)
- Biochemical and synthetic function markers: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), albumin, international normalized ratio (INR), alpha-fetoprotein (AFP), platelet count.

– *Viral infections*
Hepatitis B/C, HIV status

– *Laboratory tests*
liver function, metabolic panels

– *Current treatments*
treatment type (pharmacological and/or lifestyle-based), frequency and type of medical visits (inpatient/outpatient), and diagnostic procedures (instrumental or laboratory)

Calculated/derived fields

Based on the collected data, the following calculated and derived fields will be generated to support clinical characterization and disease staging:

– Clinical scores:
  - Child-Pugh,
  - Model for End-Stage Liver Disease (MELD),
  - FIB-4,
  - FibroScan-AST (FAST),
  - NAFLD Fibrosis Score (NFS),
  - Enhanced Liver Fibrosis (ELF);
– BMI calculation;
– Fibrosis staging (F0-F4).

The sequential data input modules for comprehensive patient assessment are shown in Figure 6.

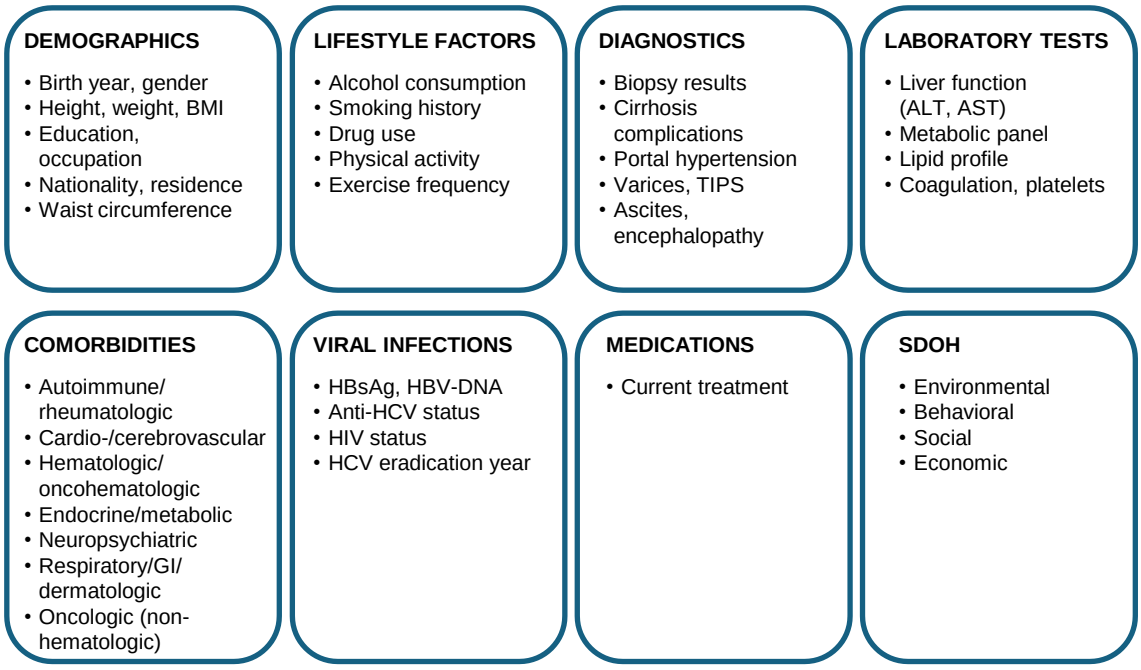

Figure 6. Data collection modules

Follow-up

Follow-up clinical data, including laboratory results and clinical events, will be recorded throughout the prospective phase using specific dedicated forms available within the platform (Follow-up eCRF).

The study includes an annual collection of follow-up information that summarizes all relevant clinical data documented during the observation period. This includes details related to the patients' care pathways, such as type of therapies, number of hospitalizations, outpatient visits, and the frequency and type of biochemical and instrumental examinations, in relation to defined clinical outcomes.

The follow-up also includes the systematic collection of the main cost drivers, including:

– Outpatient visits, differentiated by type (follow-up visit, specialist consultation) and frequency (annual, semi-annual, monthly).

– Biochemical tests with details on the number and type of tests performed.

– Instrumental procedures (including abdominal ultrasound, total body ultrasound, colour Doppler ultrasound of the portal vessels, contrast-enhanced ultrasound, transient elastography, upper gastrointestinal endoscopy (EGDS), total body computed tomography (CT) scan, abdominal CT scan, MRI, liver biopsies.

– Therapies and treatments, (including ongoing pharmacological treatments, hospitalizations (either inpatient or day hospital), surgical interventions

– The integration and combined analysis of these cost drivers will enable the estimation of the cost incurred per patient, based on the average frequency of healthcare resource utilization and the unit costs of services.

The unit costs of healthcare services will be determined based on:

- National rates established by the Outpatient Specialist Services Tariff Nomenclature (Ministerial Decree of October 18, 2012);
- Scientific literature sources;
- Real-world evidence derived from previous studies carried out by the Coordinating Unit at ISS

Record status management

Records can exist in one of the following statuses:

- *Complete:* All required data fields are filled and validated.
- *Complete (with missing data):* All feasible fields are completed; some fields are legitimately unavailable.
- *Incomplete:* Data entry is in progress; essential information is missing.

Users are encouraged to update and finalize entries as soon as data becomes available.

Data flow and validation

The platform is hosted on a certified EU-based cloud provider and complies with GDPR and international health data security standards.
All data entered by centres will:

- Remain editable by the originating centre until marked as complete.
- Generate a database file**,** obtained from the electronic platform, that will be securely transferred to the coordinating centre at ISS via protected credentials.
- Undergo both automated and manual validation procedures to ensure completeness, consistency, and accuracy of the data.

Validation checks include:

- Logical consistency across fields.
- Verification of missing values.
- Reconciliation across follow-up entries (for prospective phase).

The promoter may contact centres to clarify, revise, or complete datasets if inconsistencies are found.

Saving and security

Data saving and security measures are implemented to ensure data integrity, confidentiality, and regulatory compliance, as outlined below:

- Data are saved in real time and stored pseudonymously.
- All access is logged and traceable through audit logs.
- Datasets will be periodically downloaded and validated and analysed by the promoter

Interaction among Coordinating Centre with MASLD Clinical Centres

To ensure high-quality data collection and consistent protocol adherence across all participating sites, the Central Coordinating Centre at the ISS maintains continuous interaction with the MASLD Clinical Centres through structured training, monitoring, and technical support. Educational activities are delivered via e-learning modules, interactive webinars, and on-site or virtual training sessions targeting young investigators and clinical staff involved in the study. These initiatives are designed to strengthen familiarity with the protocol, improve consistency in eCRF completion, and foster active engagement of local teams.

Each Clinical Centre is provided with direct support from the ISS-based coordination team throughout every phase of the study, including enrolment, follow-up, and eCRF data entry. Regular annual investigator meetings, as well as scheduled teleconferences, are planned to be organized to facilitate discussion, share updates, and address emerging challenges collaboratively.

Query elaboration

Following the initial enrolment phase and completion of the corresponding eCRFs, a descriptive analysis will be conducted to assess the quality and completeness of the collected data. For each variable included in the eCRF, a predefined range of acceptable values is established. During data entry, automated controls are applied to detect and block values falling outside these predefined thresholds. This first level of verification triggers "out-of-range" queries that require prompt review and correction by the data entry personnel.

A second tier of validation consists of clinical congruency checks designed to detect inconsistencies across related clinical fields. These cross-variable queries assess logical coherence between data points, such as alignment between diagnosis and laboratory values, or consistency between reported comorbidities and administered treatments.

The integration of automated data validation, clinical logic checks, and continuous communication between the Coordinating Centre and participating Clinical Centres ensures the accuracy and integrity of both baseline and follow-up data. This collaborative and iterative approach promotes dynamic knowledge exchange and standardizes data quality across all sites, supporting the successful implementation of the ITA-MASLD study.

This rigorous data verification process is essential to enable robust and reliable statistical analyses.

Data analysis of the ITA-MASLD Cohort

The ITA-MASLD study, with its prospective design and 10-year follow-up, is designed to evaluate clinical, epidemiological, and economic outcomes associated with MASLD across different stages of liver disease, including advanced fibrosis, cirrhosis, HCC, and post-transplant status. The longitudinal structure enables analysis of the evolving epidemiologic burden over time, capturing shifts in diagnostic criteria, therapeutic approaches, and disease awareness.

The statistical analysis will proceed in two complementary phases: (1) descriptive analyses, performed continuously to monitor distributions of clinical variables, care patterns, and healthcare utilization; and (2) endpoint analyses, conducted to evaluate the study's primary and secondary objectives.

Cross-sectional endpoints will include prevalence estimates of liver-related complications, extrahepatic manifestations (e.g., cardiovascular, oncologic), and chronic or treated viral

infections (HIV, HBV, and HCV with sustained virologic response), while longitudinal endpoints will assess disease progression (e.g., changes in fibrosis stage, decompensation, HCC), hospitalization frequency, mortality, and treatment effectiveness. Analytical methods will include logistic regression for evaluating predictors of outcomes, Kaplan-Meier survival analysis with log-rank tests for survival comparisons, and Cox proportional hazards models for identifying progression and mortality predictors. Incidence rates (per 1,000 person-years) of key clinical events will also be calculated. Each model will undergo cross-validation using a random split of the cohort and a stepwise variable selection strategy to ensure robustness, with calibration and discrimination assessed via standard statistical tests.

In addition to clinical outcomes, the protocol includes a comprehensive analysis of the economic burden of the disease (COI analysis), leveraging real-world longitudinal data to quantify both direct healthcare expenditures (e.g., outpatient visits, diagnostics, treatments, hospitalizations) and indirect societal costs (e.g., productivity loss, premature mortality). Cost data will be collected through dedicated eCRFs and monetized using national tariff nomenclatures, literature sources, and prior ISS experience. Importantly, the COI component will also address the latent burden posed by the undiagnosed MASLD population. Using demographic and clinical profiles from the enrolled cohort, predictive models will simulate the characteristics and potential progression trajectories of undiagnosed individuals within the general population. These simulations will allow estimation of the unmeasured economic and health impacts of diagnostic delays or missed detection.

Scenario-based health-economic modelling, including Markov models and budget impact analysis, will be conducted to compare current standard care with hypothetical strategies such as early screening or risk-based identification. Deterministic and probabilistic sensitivity analyses will evaluate model robustness, and all evaluations will conform to international standards (e.g. Consolidated Health Economic Evaluation Reporting Standards - CHEERS). This integrated analytical approach will generate evidence to inform sustainable, equity-oriented public health policies and support the optimization of MASLD care pathways and resource allocation in Italy.

Risk analysis and solutions

The diversity in terms of geographic origin and clinical centre speciality of participating centres is designed to ensure that the patient population enrolled is representative of the broader MASLD population under clinical care. To minimize selection bias, particularly the risk of enrolling only patients with more advanced liver disease, the study protocol mandates the consecutive enrolment of all eligible patients who present at participating centres during predefined time windows, regardless of clinical severity. These enrolment windows will reopen twice a year, each lasting six consecutive months, to allow the ongoing inclusion of newly diagnosed patients and those entering care due to changes in clinical guidelines or treatment availability. As is expected with the increased disease awareness and the emergence of new treatment options, earlier diagnosis and linkage to care will improve the cohort representativeness.

The study acknowledges the limitation of the presentation of the disease clinical and economic burden based only on patients in care. However, while the study is focused on patients already within the healthcare system and cannot capture undiagnosed MASLD cases in the general population, the evaluation of data from these patients will allow the estimation of future burden of individuals yet not diagnosed. Simulating different disease scenarios based on real life data derived by the cohort, will potentially allow comparison of more than one cost-effective scenario and sustainability.

Over time, the profile of diagnosed patients and the simulated scenarios of undiagnosed population, will help to better define the real-world epidemiology of MASLD in Italy, with the

final goal of producing real life evidence for the most cost effective, sustainable health policies for diagnosis and management of MASLD and its further disease complications. Moreover, longitudinal follow-up and routine monitoring will support dynamic adjustments in data interpretation, enabling the progressive correction of any residual enrolment imbalances.

ADDRESSING MASLD INEQUITIES: MODULES AND PILOT

The ITA-MASLD study incorporates a dedicated component on SDOH. This element is designed to investigate the influence of socioeconomic, behavioural, and environmental factors on disease onset, clinical management, and long-term outcomes. By integrating this dimension, the study offers a comprehensive, multidimensional perspective on the structural and social inequities that shape MASLD care pathways.

SDOH data are collected using both clinician-reported and patient-reported instruments, enabling stratified analyses that capture disparities in healthcare access, diagnostic surveillance, and therapeutic interventions. This framework is further reinforced by a targeted pilot project on HCC equity, conducted within the Joint Action "Cancer and other NCDs prevention – action on health determinants" (PreventNCD) and supported by the ITA-MASLD infrastructure, as described below.

Understanding the role of SDOH is essential for accurately characterizing the real-world burden and trajectory of MASLD. Factors such as income level, educational attainment, employment status, housing conditions, and healthcare access exert a profound influence on individuals' exposure to metabolic risk, adherence to preventive health behaviours, and their ability to engage with timely, effective diagnostic and therapeutic services.

Given that MASLD is deeply intertwined with lifestyle and contextual determinants, analysing SDOH is fundamental to explaining the observed variability in disease burden and outcomes. Ultimately, this component supports the development of evidence-based, equity-oriented policies aimed at reducing health disparities and promoting inclusive prevention strategies across at-risk populations.

Rationale

Despite growing recognition of the importance of SDOH in noncommunicable diseases, structured and harmonized evaluations of their role in chronic liver diseases remain limited, particularly in large-scale observational cohorts.

MASLD is not only driven by biological and metabolic dysfunctions but is shaped by broader contextual factors that influence early detection, linkage to care, lifestyle modification, and treatment adherence. Barriers such as poor health literacy, economic deprivation, lack of transportation, or regional disparities in service availability contribute to delayed diagnoses and suboptimal management, particularly for individuals living in underserved or rural areas.

Recognizing this gap, the ITA-MASLD study has embedded a prospective evaluation of SDOH into its national platform. This component aims to identify population subgroups at elevated risk of disease progression or treatment exclusion due to social vulnerability. By doing so, it supports the broader objectives of the study, namely, to provide actionable real-world evidence that enhances care pathways, informs national health planning, and promotes health equity.

Objectives

The evaluation of SDOH within ITA-MASLD pursues the following objectives:

1. To systematically collect real-world data on social, economic, behavioural, and environmental factors affecting patients with MASLD across all participating centres.
2. To analyse the association between SDOH and clinical outcomes**,** including stage at diagnosis, fibrosis progression, treatment initiation, quality of life, and complications.
3. To assess regional and demographic disparities in access to care, frequency of follow-up, and use of diagnostic or therapeutic services.
4. To identify socially vulnerable patient profiles most at risk of underdiagnosis, undertreatment, or adverse outcomes.
5. To enable equity-informed policy decisions**,** through integration of SDOH in economic modelling, resource allocation frameworks, and stratified screening strategies.

SDOH variables and data collection

A dedicated SDOH module has been incorporated into the eCRF used across all ITA-MASLD centres (in Appendix A the original module in Italian is reported). Developed collaboratively with the Executive Committee and validated by clinicians and public health experts, this module allows harmonized and prospective data collection on the following dimensions:

– *Sociodemographic factors*
age, sex assigned at birth, self-identified gender, nationality, education level, household size, place of birth, and marital status.

– *Economic indicators*
employment status, income bracket (where available), job security, private transportation availability, and access to supportive services.

– *Environmental context*
postal code of residence (for linkage with national deprivation index), urban/rural status, distance to the nearest MASLD centre, and housing conditions.

– *Behavioural factors*
alcohol use, tobacco use, dietary habits, physical activity, and trust or attitudes toward the healthcare system.

– *Healthcare access*
frequency and type of outpatient visits, delays in diagnostic evaluations, difficulty in obtaining prescriptions or follow-up exams, linguistic and cultural barriers.

The data are entered at baseline and updated during annual follow-up assessments. When possible, derived indices such as the deprivation index and composite risk scores will be calculated to enable stratified analyses.

Analytical framework

The role of SDOH will be investigated through a multilevel analytical framework, combining descriptive, inferential, and predictive methods:

- Descriptive statistics will identify the prevalence and distribution of social vulnerability indicators across the national cohort.
- Multivariate regression models (logistic, Poisson, Cox) will assess the independent association of SDOH with fibrosis progression, comorbidity burden, hospitalizations, and liver-related events.
- Survival and time-to-event analyses will be conducted for major outcomes such as hepatocellular carcinoma, cirrhosis complications, and mortality.
- Stratified subgroup analyses will explore differential effects across sex, geographic macro areas, clinical centres, and age groups.
- Health economic simulations will integrate SDOH profiles to estimate the cost-effectiveness of equity-targeted interventions and to model the impact of addressing specific social vulnerabilities.

Strategic implications

The systematic evaluation of SDOH within ITA-MASLD holds transformative potential for research, clinical practice, and policy. By integrating equity into the scientific infrastructure of liver disease surveillance, ITA-MASLD sets a precedent for multidimensional cohort studies that do not merely describe disease but interrogate its context.

Findings from the SDOH component will:

- Enable more nuanced risk stratification, identifying patients who need intensified outreach or tailored interventions;
- Highlight structural barriers within the healthcare system, enabling policymakers to act on avoidable inequities;
- Support dynamic scenario modelling for national planning and resource allocation;
- Provide a foundation for international comparative research**,** particularly within WHO or EU frameworks on health equity and chronic disease prevention.

Ultimately, this initiative aims not only to document disparities, but to support a transition toward a more just, inclusive, and effective response to the growing burden of MASLD and its complications in Italy.

A critical outcome at the intersection of MASLD and social inequity: hepatocellular carcinoma

HCC is among the most severe complications of MASLD and represents one of the fastest-growing causes of cancer-related morbidity and mortality in Western countries. MASLD-related

HCC can arise in both cirrhotic and non-cirrhotic patients, often without prior liver-related symptoms, and is frequently diagnosed at an advanced stage due to lack of systematic surveillance.

As the prevalence of MASLD increases, so too does the burden of MASLD-related HCC. Recent projections suggest that MASLD will become the leading underlying cause of HCC in Italy within the next decade. Early-stage detection is crucial for access to curative therapies such as resection, ablation, or transplantation, but current screening and linkage-to-care systems are fragmented and unevenly distributed across regions.

Social determinants are deeply intertwined with these gaps. Individuals from socioeconomically disadvantaged backgrounds, rural areas, or marginalized communities face higher barriers to accessing hepatology services, imaging, and follow-up. These include reduced availability of specialized centres, transportation issues, lower awareness of liver disease, and limited continuity of care. Furthermore, mistrust in the healthcare system and low health literacy may lead to delayed symptom reporting or reluctance to undergo invasive diagnostics.

Within ITA-MASLD, HCC will be prospectively recorded and analysed as a primary longitudinal outcome. Specific aims of the HCC-SDOH subanalysis include:

- Identification of predictors of late-stage HCC diagnosis, including socioeconomic and behavioural variables;
- Evaluation of access to curative versus palliative treatments in relation to education level, residence, and support networks;
- Assessment of survival differences across social strata, adjusting for clinical covariates and treatment pathways;
- Development of risk prediction models incorporating SDOH, to refine surveillance strategies for high-risk patients.

These analyses are expected to yield critical insights for redesigning HCC screening policies and access models, shifting from uniform to equity-based approaches that recognize the interaction between clinical and social vulnerability.

Pilot evaluation of SDOH and HCC under the Joint Action PreventNCD

In support of this goal, a dedicated pilot project on liver cancer equity is being implemented under the Joint Action PreventNCD, coordinated by the ISS. This pilot focuses specifically on HCC as a tracer condition for health inequity and will use the ITA-MASLD infrastructure, its national cohort and centralized eCRF platform, as the operational backbone for data collection and analysis.

A key element of this initiative is the deployment of a digital SDOH questionnaire, available in multiple languages and accessible via QR code or web-based link. Patients enrolled in ITA-MASLD with hepatic fibrosis or a diagnosis of HCC will complete the questionnaire either directly (via smartphone or computer) or through clinical staff, depending on local context.

All responses are pseudonymized and encrypted, ensuring GDPR-compliant data protection and no identifiability. The data are integrated with clinical indicators such as fibrosis stage, HCC status, treatment received, and survival outcomes, allowing multi-dimensional analysis of how SDOH influence the entire HCC care continuum, from surveillance to treatment response and long-term prognosis.

By embedding this pilot within the ITA-MASLD framework, Italy becomes a leading case study in applying structured SDOH data collection and ethical health equity evaluation in real-

world chronic disease cohorts. The pilot will deliver evidence to inform both national guidelines and European cancer control strategies, aiming to reduce disparities and improve outcomes in MASLD-related liver cancer.

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APPENDIX A
eCRF in Italian

Studio Osservazionale ITA-MASLD

Codice scheda: **M00081**

QUESTIONARIO Social Determinants of Health (SDoH)

Data visita: gg mm aaaa

1 Luogo di nascita:

2 Cittadinanza:
- ○ Italia
- ○ Estero

Se estero, specificare Paese:

3 Se straniero, da quanti anni in Italia:
specificare

4 CAP di domicilio:

5 Livello di istruzione:
- ○ Licenza elementare
- ○ Licenza media
- ○ Licenza secondaria superiore
- ○ Laurea
- ○ Titoli post-universitari
- ○ Altro

specificare

6 Lingue conosciute:
- ☐ Italiano
- ☐ Inglese
- ☐ Francese
- ☐ Spagnolo
- ☐ Tedesco
- ☐ Arabo
- ☐ Cinese
- ☐ Russo
- ☐ Altra

specificare

7 Lingua parlata in famiglia:
- ☐ Italiano
- ☐ Inglese
- ☐ Francese
- ☐ Spagnolo
- ☐ Tedesco
- ☐ Arabo
- ☐ Cinese
- ☐ Russo
- ☐ Dialetto locale
- ☐ Altra

specificare

8 Qual è la Sua condizione professionale?
- ○ Lavoratore/lavoratrice
- ○ Disoccupato/a
- ○ Non forze di lavoro (non occupato/a né in cerca di occupazione)
- ○ Pensionato/a

9 Attività lavorativa (in caso di più attività inserire la principale):

aggiungi

10 Stato civile:
- ○ Celibe/Nubile
- ○ Coniugato/a
- ○ Convivente
- ○ Separato/a
- ○ Divorziato/a
- ○ Vedovo/a

11 Ha una relazione sentimentale stabile? (Per relazione stabile si intende una relazione affettiva continuativa e attualmente in corso, anche se non convivente)
- ○ No
- ○ Sì
- ○ Preferisco non rispondere

12 In che tipo di abitazione vive?
- ○ Abitazione privata
- ○ Casa di cura
- ○ Comunità

13 Quante persone vivono con Lei? (Indichi il numero di conviventi per fascia d'età)
- ☐ Adulti con età maggiore di 70 anni:
- ☐ Adulti con età compresa tra 46 e 70 anni:
- ☐ Adulti con età compresa tra 18 e 45 anni:
- ☐ Adolescenti e bambini:
- ☐ Vivo da solo/a

14 Tipologia di conviventi:
- ☐ Familiari/congiunti
- ☐ Coinquilini

15 È in possesso di un mezzo di trasporto autonomo?
- ○ No
- ○ Sì

16 Se sì, quale?
- ☐ Auto
- ☐ Motocicletta
- ☐ Bicicletta/altro

Consumo di alcool

17 Ha fatto uso o fa uso di Alcool?
- ○ Astemio
- ○ Sì, attualmente
- ○ Sì, in passato

18 Ha fatto uso o fa uso di vino? ○ No ○ Sì

19 Consumo settimanale di vino:

20 Ha fatto uso o fa uso di birra? ○ No ○ Sì

21 Consumo settimanale di birra:

22 Ha fatto uso o fa uso di superalcolici? ○ No ○ Sì

23 Consumo settimanale di superalcolici:

Consumo di tabacco

24 Fuma sigarette attualmente?
- ○ No, non ho mai fumato
- ○ No, ma ho fumato in passato
- ○ Sì

25 Se fuma o ha fumato in passato, quante sigarette in media al giorno?

Consumo di sigarette elettroniche

26 Fuma mediante dispositivo elettronico attualmente?
- ○ No, non ho mai fumato
- ○ No, ma ho fumato in passato
- ○ Sì

Esercizio fisico

27 Quante volte alla settimana svolge attività fisica moderata o intensa? (Per attività fisica moderata o intensa si intendono attività che fanno aumentare il respiro e la frequenza cardiaca rispetto al riposo e che possono provocare sudorazione, es. camminata a passo svelto, corsa, bicicletta, nuoto, sport o altre attività simili)

- ○ Mai
- ○ 1-2 volte
- ○ 3-4 volte
- ○ 5 o più volte

28 Per quanto tempo pratica attività fisica in media ogni volta?

- ○ Meno di 30 minuti
- ○ 30-60 minuti
- ○ Più di 60 minuti

29 Ci sono fattori che La ostacolano nello svolgimento di una regolare attività fisica? (se sì, indichi il principale)

- ○ Nessun ostacolo
- ○ Mancanza di tempo
- ○ Mancanza di spazi o strutture adeguate
- ○ Costi
- ○ Mancanza di motivazione
- ○ Altro

specificare

Cura dell'alimentazione

30 Quanti pasti principali (colazione, pranzo, cena) si può permettere al giorno?

- ○ 1
- ○ 2
- ○ 3

31 Quali pasti principali mediamente consuma al giorno?

- ☐ Colazione
- ☐ Pranzo
- ☐ Cena

32 Con quale frequenza consuma frutta, verdura e altri cibi freschi preparati al momento (non confezionati, non precotti, non da fast food)?

- ○ Ogni giorno
- ○ 4-6 volte a settimana
- ○ 1-3 volte a settimana
- ○ Meno di una volta a settimana (es. 1 volta al mese)
- ○ Mai

33 Con che frequenza consuma cibi considerati non salutari (fast food, cibi confezionati/precotti, snack e dolciumi)?

- ○ Ogni giorno
- ○ 4-6 volte a settimana
- ○ 1-3 volte a settimana
- ○ Meno di una volta a settimana (es. 1 volta al mese)
- ○ Mai

34 Ci sono fattori che la ostacolano nel seguire un'alimentazione sana (cibi sani e freschi)? (Se sì, indichi il principale)

- ○ Nessun ostacolo
- ○ Costo
- ○ Tempo
- ○ Mancanza di conoscenze
- ○ Altro

specificare

35 Quanto ritiene che una buona alimentazione e l'attività fisica influiscano sulla sua salute generale?

- ○ Per nulla
- ○ Poco
- ○ Abbastanza
- ○ Molto

Deprivazione materiale

36 Negli ultimi 12 mesi, ci sono stati momenti o periodi in cui Lei/la Sua famiglia è stato/a in arretrato con il pagamento delle bollette, ad esempio, quelle per il condominio, l'acqua, il gas o l'elettricità, per mancanza di soldi? Non consideri le bollette telefoniche.
- ○ Sì
- ○ No
- ○ Preferisco non rispondere

37 Negli ultimi 12 mesi, ci sono stati momenti o periodi in cui Lei/la Sua famiglia è stato/a in arretrato con il pagamento dell'affitto dell'abitazione o delle rate del mutuo per mancanza di soldi?
- ○ Sì
- ○ No
- ○ Preferisco non rispondere

38 Negli ultimi 12 mesi, Lei o qualcuno della Sua famiglia è stato/a in arretrato con il rimborso di prestiti ricevuti da banche e/o società finanziarie per mancanza di soldi? Includa soltanto prestiti per ristrutturazione o acquisto di abitazioni secondarie, mobili, automobili o altri beni. Non consideri eventuali mutui o prestiti per acquistare o ristrutturare l'abitazione principale.
- ○ Sì
- ○ No
- ○ Preferisco non rispondere

39 Tenendo conto di tutti i redditi disponibili, Lei/la Sua famiglia come riesce ad arrivare alla fine del mese?
- ○ Con grande difficoltà
- ○ Con difficoltà
- ○ Con qualche difficoltà
- ○ Con una certa facilità
- ○ Con facilità
- ○ Con molta facilità
- ○ Preferisco non rispondere

40 Lei/la Sua famiglia sarebbe in grado di far fronte, con risorse proprie, a spese impreviste di un ammontare approssimativo di 1.000 euro?
- ○ Sì
- ○ No
- ○ Preferisco non rispondere

41 Lei/la Sua famiglia, se volesse, potrebbe permettersi di riscaldare adeguatamente l'abitazione in cui vive?
- ○ Sì
- ○ No
- ○ Preferisco non rispondere

Indichi il Suo grado di accordo/disaccordo per ciascuna affermazione

(1 = fortemente in disaccordo, 2 = in disaccordo, 3 = tendenzialmente in disaccordo, 4 = tendenzialmente in accordo, 5 = in accordo, 6 = fortemente in accordo)

1. La medicina si basa su principi scientifici
   ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6
2. Il miglioramento della salute di una nazione è dovuto a una medicina efficace
   ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6
3. La medicina ha trattamenti per la maggior parte dei disturbi
   ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6
4. La medicina è la migliore professione che una persona potrebbe avere
   ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6
5. Le medicine possono fare tanto male quanto bene
   ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6
6. Il consiglio dei medici è principalmente il buon senso
   ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6
7. Molte medicine sono semplicemente placebo o pillole di zucchero
   ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6
8. Spesso l'unico scopo degli esami è far sentire un medico meno ansioso
   ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6
9. La maggior parte degli esami e delle indagini viene eseguita di routine piuttosto che per uno scopo particolare
   ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6

FACT-Hep (Version 4)

Sotto abbiamo elencato delle affermazioni ritenute importanti da persone con la Sua stessa malattia.

La preghiamo di cerchiare o contrassegnare un solo numero per riga per indicare la Sua risposta in riferimento agli ultimi 7 giorni.

	BENESSERE FISICO	**Per niente**	**Un po'**	**Abbastanza**	**Molto**	**Moltissimo**
GP1	Mi manca l'energia	○	○	○	○	○
GP2	Ho nausea	○	○	○	○	○
GP3	Ho difficoltà ad occuparmi delle necessità della mia famiglia a causa delle mie condizioni fisiche	○	○	○	○	○
GP4	Ho dolori	○	○	○	○	○
GP5	Mi danno fastidio gli effetti collaterali della cura	○	○	○	○	○
GP6	Mi sento male	○	○	○	○	○
GP7	Sono costretto/a a trascorrere del tempo a letto	○	○	○	○	○
		Per	**Un**			

BENESSERE SOCIALE/FAMILIARE		Per niente	Un po'	Abbastanza	Molto	Moltissimo
GS1	Mi sento vicino/a ai miei amici	○	○	○	○	○
GS2	La mia famiglia mi sostiene moralmente	○	○	○	○	○
GS3	Ho appoggio morale dai miei amici	○	○	○	○	○
GS4	La mia famiglia ha accettato la mia malattia	○	○	○	○	○
GS5	Sono soddisfatto/a della comunicazione nella mia famiglia a proposito della mia malattia	○	○	○	○	○
GS6	Mi sento vicino/a al mio compagno/alla mia compagna (o alla persona che mi offre il maggiore appoggio)	○	○	○	○	○
Q1	Indipendentemente dalla Sua attività sessuale, la preghiamo di rispondere alla seguente domanda. Se preferisce non rispondere, barri questa casella e passi alla prossima sezione.	☐				
GS7	Sono soddisfatto/a della mia attività sessuale	○	○	○	○	○

BENESSERE EMOTIVO		Per niente	Un po'	Abbastanza	Molto	Moltissimo
GE1	Mi sento triste	○	○	○	○	○
GE2	Sono soddisfatto/a di come sto affrontando la mia malattia	○	○	○	○	○
GE3	Sto perdendo la speranza nella lotta contro la mia malattia	○	○	○	○	○
GE4	Sono nervoso/a	○	○	○	○	○
GE5	Mi preoccupo al pensiero della morte	○	○	○	○	○
GE6	Mi preoccupo che le mie condizioni possano peggiorare	○	○	○	○	○

BENESSERE FUNZIONALE		Per niente	Un po'	Abbastanza	Molto	Moltissimo
GF1	Sono in grado di lavorare (si intende anche il lavoro a casa)	○	○	○	○	○
GF2	Il mio lavoro (si intende anche il lavoro a casa) mi gratifica	○	○	○	○	○
GF3	Riesco a godermi la vita	○	○	○	○	○
GF4	Ho accettato la mia malattia	○	○	○	○	○

GF5	Dormo bene	○	○	○	○	○
GF6	Provo ancora piacere nel dedicarmi ad attività di tempo libero	○	○	○	○	○
GF7	Al momento, sono soddisfatto/a della qualità della mia vita	○	○	○	○	○

	ULTERIORI PROBLEMI	**Per niente**	**Un po'**	**Abbastanza**	**Molto**	**Moltissimo**
C1	Ho gonfiore o crampi all'addome	○	○	○	○	○
C2	Sto dimagrendo	○	○	○	○	○
C3	Riesco a controllare le mie funzioni intestinali	○	○	○	○	○
C4	Digerisco bene ciò che mangio	○	○	○	○	○
C5	Soffro di diarrea	○	○	○	○	○
C6	Il mio appetito è buono	○	○	○	○	○
Hep1	Il cambiamento nel mio aspetto mi fa sentire a disagio	○	○	○	○	○
CNS7	Mi fa male la schiena	○	○	○	○	○
Cx6	Mi dà fastidio avere problemi di stitichezza	○	○	○	○	○
HI7	Mi sento affaticato/a	○	○	○	○	○
An7	Sono in grado di svolgere le mie attività abituali (lavorare, andare a scuola, fare la spesa, svolgere attività durante il tempo libero, ecc.)	○	○	○	○	○
Hep2	Sono infastidito/a dall'itterizia o dal mio colorito giallastro	○	○	○	○	○
Hep3	Ho avuto episodi febbrili	○	○	○	○	○
Hep4	Ho avuto prurito	○	○	○	○	○
Hep5	Il sapore dei cibi mi sembra cambiato	○	○	○	○	○
Hep6	Ho avuto brividi	○	○	○	○	○
HN2	Ho la bocca secca	○	○	○	○	○
Hep8	Ho fastidi o dolori all'addome	○	○	○	○	○


STATO DELLA SCHEDA
La scheda è da considerarsi:
Completa
Non completa
Completa anche se alcuni dati sono mancanti

Salva
Annulla

APPENDIX B
SDOH questionnaire in Italian*

*The English version of the questionnaire can be provided upon request

ITA-MASDL - Questionario sui determinanti sociali della salute

1. In quale Paese è nato/a?

- ❑ Italia
- ❑ Altro Paese (specificare): _____

2. Qual è la Sua cittadinanza?

- ❑ Italiana
- ❑ Altro paese UE
- ❑ Extra-UE
- ❑ Altro: _____

3. Se non è nato/a in Italia, da quanti anni vive in Italia?

- ❑ __ anni (numero)

4. Può indicarci il CAP (Codice di Avviamento Postale) del suo domicilio (il luogo in cui abitualmente vive)?

_____ (numero, 5 cifre)

5. Qual è il più alto livello di istruzione che ha completato?

- ❑ Nessun titolo di studio / Scuola elementare non conclusa
- ❑ Licenza elementare (Scuola primaria)
- ❑ Licenza media (Scuola secondaria di I grado)
- ❑ Diploma di scuola superiore (Scuola secondaria di II grado)
- ❑ Laurea o titolo terziario (es. laurea triennale, magistrale)
- ❑ Dottorato o specializzazione post-laurea

6. Qual è la Sua situazione lavorativa attuale?

- ❑ Occupato/a
- ❑ Disoccupato/a (in cerca di lavoro)
- ❑ Non forze di lavoro
  (non occupato/a né in cerca di occupazione, es.: studente/essa, caregiver, casalinga/o)
- ❑ Pensionato/a

7. Che tipo di lavoro svolge attualmente o svolgeva al momento del pensionamento?

- ❑ Dirigenti, imprenditori, liberi professionisti (es. manager, imprenditori, medici, avvocati, ingegneri, ecc.)
- ❑ Impiegati e tecnici (es. impiegati amministrativi, insegnanti, tecnici, infermieri, operatori sanitari qualificati, ecc.)
- ❑ Commercianti, artigiani e lavoratori dei servizi (es. commessi, camerieri, parrucchieri, autisti, artigiani, agricoltori, ecc.)
- ❑ Operai e lavoratori non qualificati (es. operai generici, addetti alle pulizie, manovali, ecc.)

8. Qual è il Suo stato civile attuale?

- ❑ Celibe/Nubile (mai sposato/a)
- ❑ Sposato/a
- ❑ Convivente (unione civile/ di fatto)
- ❑ Separato/a o divorziato/a
- ❑ Vedovo/a

9. In che tipo di abitazione vive?

- ❑ Abitazione privata
- ❑ Casa di cura
- ❑ Alloggio temporaneo/Comunità
- ❑ Altro

10. Quante persone vivono con Lei? (Indichi il numero di conviventi per fascia d'età)

- ❑ Adulti con età maggiore di 70 anni: N._____
- ❑ Adulti con età compresa tra 46 e 70 anni: N._____
- ❑ Adulti con età compresa tra 18 e 45 anni: N._____
- ❑ Adolescenti e bambini: N._____
- ❑ Vivo da solo/a

11. Negli ultimi 12 mesi, Le è capitato di rinunciare o rimandare una visita o un trattamento medico necessario?

- ❑ Sì
- ❑ No

12. Se Sì, qual è stato il motivo principale?

- ❑ Costo
- ❑ Lista d'attesa
- ❑ Motivi familiari
- ❑ Distanza/Trasporto
- ❑ Lavoro
- ❑ Altro

13. Tenendo conto di tutti i redditi disponibili, Lei/la Sua famiglia come riesce ad arrivare alla fine del mese?

- ❑ Con grande difficoltà
- ❑ Con difficoltà
- ❑ Con qualche difficoltà
- ❑ Con una certa facilità
- ❑ Con facilità
- ❑ Con molta facilità

14. Lei/la Sua famiglia, se volesse, potrebbe permettersi di riscaldare adeguatamente l'abitazione in cui vive?

- ❑ Sì
- ❑ No

15. Lei/la Sua famiglia sarebbe in grado di far fronte, con risorse proprie, a spese impreviste di un ammontare approssimativo di 1.000 euro?

- ❑ Sì
- ❑ No

Negli ultimi 12 mesi, per mancanza di soldi o di altre risorse, a Lei o a qualcuno della Sua famiglia è capitato:

16. di essere preoccupato/a di non avere abbastanza cibo da mangiare ❑ Sì ❑ No

17. di non aver potuto mangiare del cibo salutare e nutriente ❑ Sì ❑ No

18. di aver mangiato solo alcuni tipi di cibo ❑ Sì ❑ No

19. di aver dovuto saltare un pasto ❑ Sì ❑ No

20. di aver mangiato meno di quanto pensava avrebbe dovuto ❑ Sì ❑ No

21. Pensando nuovamente agli ultimi 12 mesi, per mancanza di soldi o di altre risorse, a Lei/alla Sua famiglia è capitato di aver esaurito il cibo:

- ❑ Sì
- ❑ No

Sempre pensando agli ultimi 12 mesi, per mancanza di soldi o di altre risorse, a Lei o a qualcuno della Sua famiglia è capitato:

22. di aver avuto fame e non aver potuto mangiare ❑ Sì ❑ No

23. di non aver mangiato per un giorno intero ❑ Sì ❑ No

24. Con riferimento ad una settimana tipo della stagione attuale, Lei quanto spesso consuma frutta fresca o secca? Escluda i succhi di frutta confezionati.

- ❑ Due o più volte al giorno
- ❑ Una volta al giorno
- ❑ 4-6 volte a settimana
- ❑ 1-3 volte a settimana
- ❑ Meno di una volta a settimana (es. 1 volta al mese)
- ❑ Mai

25. Con riferimento ad una settimana tipo della stagione attuale, Lei quanto spesso mangia verdura o insalata? Escluda le patate.

- ❑ Due o più volte al giorno
- ❑ Una volta al giorno
- ❑ Da 4 a 6 volte a settimana
- ❑ Da 1 a 3 volte a settimana
- ❑ Meno di una volta a settimana (es. 1 volta al mese)
- ❑ Mai

26. Con riferimento ad una settimana tipo della stagione attuale, Lei quanto spesso consuma cibi considerati non salutari (fast food, cibi confezionati/precotti, snack e dolciumi)?

- ❑ Due o più volte al giorno
- ❑ Una volta al giorno
- ❑ Da 4 a 6 volte a settimana
- ❑ Da 1 a 3 volte a settimana
- ❑ Meno di una volta a settimana (es. 1 volta al mese)
- ❑ Mai

27. Ci sono fattori che la ostacolano nel seguire un'alimentazione sana (cibi sani e freschi)? Se sì, indicare il principale

- ❑ No, nessun ostacolo
- ❑ Sì, costi elevati
- ❑ Sì, mancanza di tempo
- ❑ Sì, mancanza di conoscenze

28. Negli ultimi 12 mesi Lei ha consumato bevande alcoliche (birra, vino, superalcolici, liquori, amari, aperitivi alcolici, ecc.)?

- ❑ Sì, tutti i giorni
- ❑ Sì qualche volta a settimana
- ❑ Sì, qualche volta al mese
- ❑ Sì, qualche volta all'anno
- ❑ No, mai

29. Attualmente, fuma tabacco ogni giorno, meno di ogni giorno, oppure per nulla?

- ❑ Ogni giorno
- ❑ Meno di ogni giorno
- ❑ Per nulla
- ❑ Non so

30. Ha fumato tabacco tutti i giorni in passato?

- ❑ Sì
- ❑ No
- ❑ Non so

31. In passato, ha fumato tabacco ogni giorno, meno di ogni giorno, oppure per niente?

- ❑ Ogni giorno
- ❑ Meno di ogni giorno
- ❑ Per nulla
- ❑ Non so

32. In una settimana tipo, Lei quanto spesso si dedica ad attività fisica moderata o intensa?
Faccia riferimento alle attività che Lei pratica continuativamente per almeno 10 minuti e che comportano almeno un leggero aumento della frequenza respiratoria o cardiaca, come ad esempio camminare a passo sostenuto, andare in bicicletta, nuotare

- ❑ Due o più volte al giorno
- ❑ Una volta al giorno
- ❑ Da 4 a 6 volte a settimana
- ❑ Da 1 a 3 volte a settimana
- ❑ Meno di una volta a settimana (es. 1 volta al mese)
- ❑ Mai

33. Per quanto tempo pratica attività fisica in media ogni volta?

- ❑ Meno di 30 minuti
- ❑ 30-60 minuti
- ❑ Più di 60 minuti

34. Ci sono fattori che la ostacolano nello svolgimento di una regolare attività fisica?

- ❑ No, nessun ostacolo
- ❑ Sì, mancanza di tempo
- ❑ Sì, costi elevati, mancanza di spazi o strutture adeguate

35. Quanto ritiene che una buona alimentazione e l'attività fisica influiscano sulla sua salute generale?

- ❑ Per nulla
- ❑ Poco
- ❑ Abbastanza
- ❑ Molto

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