United European Gastroenterology Journal

WILEY

UNITED EUROPEAN GASTROENTEROLOGY ueg journal

ORIGINAL ARTICLE OPEN ACCESS

Nodular Regenerative Hyperplasia: Report of 82 Patients and Systematic Review of Literature

Edeline Kaze[1] | Pamela Baldin[2] | Hubert Piessevaux[3] | Géraldine Dahlqvist[3]

[1]Department of Gastroenterology and Hepatology, Europe Hospitals, Brussels, Belgium | [2]Department of Pathology, Cliniques Universitaires Saint-Luc, Brussels, Belgium | [3]Department of Gastroenterology and Hepatology, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Correspondence: Géraldine Dahlqvist (geraldine.dahlqvist@saintluc.uclouvain.be)

Received: 3 April 2024 | **Revised:** 29 September 2024 | **Accepted:** 11 October 2024

Funding: The authors received no specific funding for this work.

Keywords: diagnosis | liver biopsy | nodular regenerative hyperplasia | portal hypertension | porto-sinusoidal vascular disorder

ABSTRACT

Background: Data about the clinical significance and outcome of patients with nodular regenerative hyperplasia are limited.

Objective: The aim of this study was to describe the clinical and histopathological characteristics of patients with nodular regenerative hyperplasia and compare our findings with the literature.

Methods: From January 2015 to March 2021, patients with a diagnosis of nodular regenerative hyperplasia were included. They were extracted from the database of the pathology department of Cliniques universitaires Saint-Luc. Clinical and histological data were retrospectively recorded and complications of portal hypertension and mortality were analyzed. We also performed a systematic review of the literature.

Results: Eighty-two histology-proven nodular regenerative hyperplasia were included. The mean age at diagnosis was 58 ± 14 years. At least one clinical sign of portal hypertension was present in 37 patients (45%), and liver tissue sampling was performed for 29 of them for evaluation of portal hypertension. Conversely, nodular regenerative hyperplasia was an incidental discovery in 27 patients (33%), mostly after liver resection for metastasis ($n = 15$) or protocol biopsy in liver-transplanted patients ($n = 9$). The 5-year liver-related mortality was 5%. The 5-year non-liver-related mortality was 20%. Patients diagnosed by clinical suspicion ($n = 55$) were compared to patients diagnosed incidentally ($n = 27$). Patients with an incidental diagnosis had more frequently a condition associated with nodular regenerative hyperplasia than patients diagnosed clinically (93% vs. 66%, $p = 0.008$) and they developed significantly lower liver-related complications (4% vs. 27%, $p = 0.01$). A systematic review allowed us to compare our patients with 10 case series in the literature.

Conclusion: The clinical spectrum of patients with nodular regenerative hyperplasia is heterogeneous, including patients with clinical liver manifestations and patients diagnosed incidentally who could remain free of liver-related complications. This suggests that nodular regenerative hyperplasia could be a histological epiphenomenon as well as a clinical entity.

Abbreviations: Alk Phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, g-glutamyltransferase; H&E, hematoxylin and eosin; HCC, hepatocellular carcinoma; INR, international normalized ratio; NRH, nodular regenerative hyperplasia; PSVD, porto-sinusoidal vascular disorder; SOS, sinusoidal obstruction syndrome Structured; TIPS, transjugular intrahepatic porto-systemic shunt; VALDIG, Vascular Liver Disease Interest Group.

Summary

- Summarise the established knowledge on this subject
  - Patients with NRH mainly present with signs of portal hypertension
  - According to autopsy series, some patients are asymptomatic
  - The clinical significance of NRH is therefore uncertain
- What are the significant and/or new findings of this study?
  - This is the first study to include patients with NRH diagnosed incidentally. This point makes the originality of the current study.
  - Our incidental cases of NRH occurred mainly in the setting of liver transplantation or liver resection for metastasis
  - These patients did not develop portal hypertension-related complications
  - This suggests that NRH could be a histological epiphenomenon as well as a clinical entity.
  - The natural history of incidental NRH remains unknown and should be studied.

1 | Introduction

Nodular regenerative hyperplasia (NRH) is a histological lesion characterized by micronodular transformation of the liver in the absence of significant fibrosis [1]. NRH was first described in 1953 by Ranstrom under the designation of miliary hepatocellular adenomatosis [2, 3]. According to consecutive autopsy series, its prevalence varies between 2.1% and 2.6% [4, 5]. NRH belonged previously to the histological features reported in patients with idiopathic (non-cirrhotic) portal hypertension [6]. In 2019, the Vascular Liver Disease Interest Group (VALDIG) proposed to replace the term "idiopathic portal hypertension" by porto-sinusoidal vascular disease, which later became porto-sinusoidal vascular disorder (PSVD), in order to group into a common entity three pivotal histological lesions observed in patients with idiopathic portal hypertension: NRH, obliterative portal venopathy and incomplete septal fibrosis [7–9].

Even though NRH has been known for 70 years, it remains a particularly mysterious lesion. First, multiple conditions have been associated with NRH without an obvious common etiology [10]. Second, its pathogenesis is not clearly understood. It seems to be related to abnormalities in the blood flow [11], but the reason why and how this histological lesion occurs is largely unknown. Third, it remains unexplained why some patients develop clinical portal hypertension [12] while others remain asymptomatic and are diagnosed incidentally [13]. Fourth, the natural history of NRH is poorly known and is limited to a few cases series [13–15]. Fifth, the outcome of patients with asymptomatic NRH has not been studied. Lastly, the association of NRH with the two other pivotal lesions of PSVD, obliterative portal venopathy and incomplete septal fibrosis, has not been elucidated.

Accordingly, our aim was to contribute to the knowledge of this curious entity. For this, we explored the clinical and histopathological characteristics and outcomes of our patients with NRH. We also compared our findings with those in the literature.

2 | Materials and Methods

2.1 | Patient Selection and Histological Assessment

Cases of NRH were retrospectively collected from the database of the pathology department of Cliniques universitaires Saint-Luc. Histological reports including the following terms "nodular regenerative hyperplasia" from January 2015 to March 2021 were identified. Only those with a confirmed diagnosis of NRH in the conclusion of the histological report were selected. Patients under 18-year-old and those with insufficient information in their medical records were excluded. Formalin-fixed and paraffin-embedded core biopsies and resection specimens were reviewed by the same expert liver pathologist (P.B.) according to the guidelines [5, 11]. Hematoxylin and eosin (H&E), reticulin staining and CK7 immunostained slides were evaluated. NRH was graded according to the Wanless scoring system: 0, absent; 1, nodules present on reticulin staining but indistinct; 2, nodules present on reticulin staining but only occasionally distinct; and 3, nodules distinctly visible on H&E [5]. Biopsy size (only for core biopsy), number of portal tracts (only for core biopsy), portal inflammation, lobular inflammation, sinusoidal dilatation, and the presence of cholestasis were reported. Fibrosis was assessed using Venturi [16] and Metavir scores. The presence of histological signs of PSVD (specific and non-specific) were evaluated as well as the presence of sinusoidal obstruction syndrome (SOS). Finally, only liver biopsies considered adequate according to guidelines were analyzed [7].

2.2 | Data Collection and Outcomes

Demographical, laboratory, clinical, imaging, and endoscopic data at diagnosis were retrospectively extracted from the medical records. Indications for liver specimens and conditions associated with NRH were also collected. Conditions associated with NRH were categorized as drug exposure, immunological disorders, genetic disorders, hemocoagulative disorders and cardiovascular diseases [10, 17]. Follow-up began at the histological diagnosis of NRH and ended on March 31, 2022. Concerning the follow-up, the primary endpoint was the development of portal hypertension-related complications. Secondary endpoints were liver-related and non-liver related mortality. Furthermore, patients were classified as "incidental NRH" when NRH was unexpected or unsuspected prior to the histological diagnosis of NRH. In those cases, histological assessment of the liver was not performed because of clinical suspicion of NRH. On the contrary, patients were classified as "clinical NRH" when NRH was expected or suspected based on clinical, biological and/or morphological signs prior to the histological diagnosis.

2.3 | Statistical Analyses

Statistical analysis was performed using SPSS Statistics 28.0.1.1 (IBM Corp, Armonk, NY). Continuous variables were presented as mean and discrete variables as number and percentage. Categorical variables were analyzed using the chi-square test and continuous variables using the Student's *t*-test. A *p*-

value < 0.05 was considered significant. Kaplan–Meier survival analysis was used to evaluate the survival and the complication-free survival.

2.4 | Systematic Review of the Literature

To compile data of the literature comparable with our methodology and findings, we conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18] (see Supporting Information S1). We included consecutive case series of patients with NRH identified from a pathology database and occurring in an adult general population. Patients were identified exclusively from a pathology database in order to highlight the clinical significance of NRH. Therefore, case series from patients diagnosed solely from a clinical database were excluded. We also excluded series that evaluated the occurrence of NRH in patients with an underlying disease or condition in order to rule out studies that did not address our research question. Finally, we excluded case series reporting less than 10 cases to avoid the inclusion of case reports.

3 | Results

3.1 | Selection of Cases and Baseline Characteristics

The flowchart of included patients is reported in Figure 1. We included 82 patients. The clinical characteristics of these patients are reported in Table 1. The mean age at diagnosis was 58 ± 14 years. Conditions associated with NRH were identified in 61 patients (74%). Forty-six patients (56%) had a history of exposure to immunosuppressive or antineoplastic drugs. Four patients (5%) had an immunological disorder, two patients (2%) a genetic disease, five patients (6%) a cardiovascular disease and four patients (5%) a hemocoagulative condition. In 21 patients (26%), no conditions associated with NRH could be identified.

At diagnosis, 37 patients (45%) had at least one clinical sign of portal hypertension. Among them, 30 patients (37%) had splenomegaly (with thrombocytopenia in 63% of them), 16 patients (19%) had ascites and 23 patients (28%) esophageal varices. Moreover, three patients (4%) had a portal vein thrombosis or mesenteric vein thrombosis. In one patient, NRH was diagnosed at the same time as hepatocellular carcinoma (HCC). Hepatic venous pressure gradient was performed in 44 patients (54%). The mean value was 7 ± 4 mm Hg. Liver stiffness measurements determined by transient elastography (Fibroscan) were performed in 18 patients. The mean value was 12 ± 10 kPa (Table 1). Liver tests at diagnosis are reported in Table 1. At inclusion, 65 patients (79%) had at least one abnormal liver biological test.

3.2 | Histological Characteristics

As reported in Table 2, among the 82 patients of our study, 29 patients (35%) had a liver biopsy for evaluation of portal hypertension and 20 patients (24%) for abnormal liver tests. Interestingly, NRH was diagnosed incidentally in 27 patients (33%): 18 patients underwent liver resection or liver biopsy for liver tumors: metastasis (15 patients), cholangiocarcinoma (1 patient), hepatocellular adenoma (1 patient), non-cirrhotic HCC (1 patient) and 9 patients had a protocol biopsy after liver transplantation.

Most liver specimens were obtained by needle liver biopsy: transjugular liver biopsy was performed in 46 patients (56%), percutaneous liver biopsy in 17 patients (21%) and intraoperative

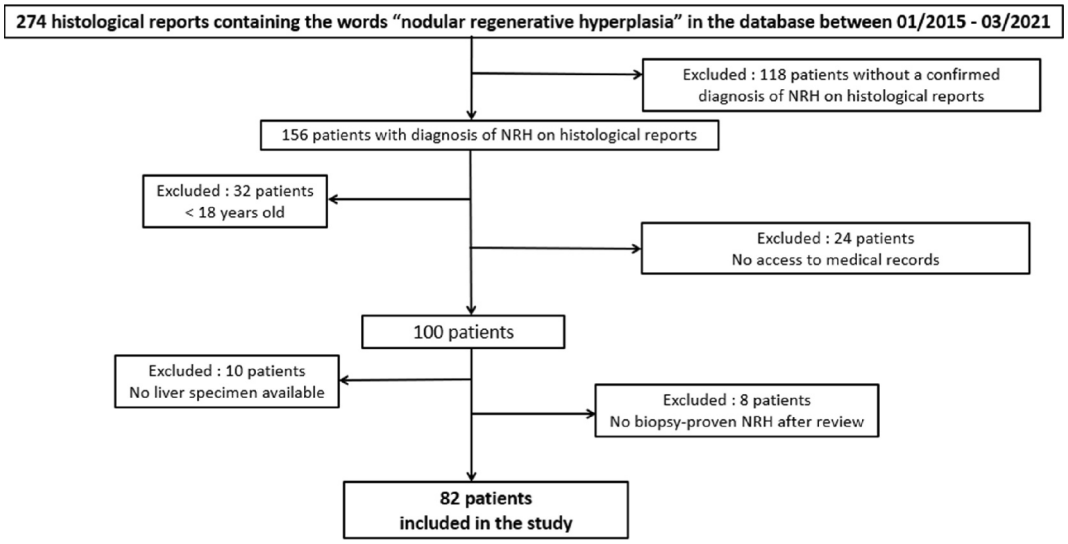

FIGURE 1 | Flowchart. From the database of our pathology department, 274 cases were evaluated. 118 cases were rapidly excluded because NRH was not retained as a diagnosis in the histological report. 66 other cases were also excluded. Finally, after a review of 90 slides by an expert liver pathologist (P.B.), 82 patients were included.

TABLE 1 | Baseline characteristics in 82 NRH patients.

Demographical characteristics	
Sex (men), *n* (%)	49 (60%)
Mean age at diagnosis (years ± SD)	58 ± 14
Conditions associated with NRH	
Drug exposure (immunosupressive or antineoplastic drug)[a], *n* (%)	46 (56%)
Immunological disorder[b], *n* (%)	4 (5%)
Genetic disorder[c], *n* (%)	2 (2%)
Cardiovascular disease[d], *n* (%)	5 (6%)
Hemocoagulative disorder[e], *n* (%)	4 (5%)
No associated conditions identified, *n* (%)	21 (26%)
Liver-related characteristics at diagnosis	
Splenomegaly, *n* (%)	30 (37%)
Thrombocytopenia, *n* (%)	23 (28%)
Ascites, *n* (%)	16 (19%)
Esophageal varices, *n* (%)	23 (28%)
Presence of portal vein thrombosis/mesenteric vein thrombosis, *n* (%)	3 (4%)
Hepatocellular carcinoma, *n* (%)	1 (1%)
Hepatic venous pressure gradient[f] (mean mm Hg ± SD)	7 ± 4 (in 44 cases)
Liver stiffness measurement[g] (mean kPa ± SD)	12 ± 10 (in 18 cases)
Liver-related laboratory findings at diagnosis	
AST (U/L) (normal range 15–40)	63 ± 113
ALT (U/L) (normal range 10–40)	70 ± 154
GGT (U/L) (normal value < 60)	173 ± 252
Alk Phos[h] (U/L) (normal range 40–130)	168 ± 186
Bilirubin[h] (mg/dL) (normal value < 1.2)	0.77 ± 0.5
Albumin[i] (mg/dL) (normal range 35–52)	40 ± 7
INR[j] (0.80–1.20)	1.16 ± 0.3
Albumin-bilirubine[i] (ALBI) score	−2.7 ± 0.6
Platelets[h] (109/L) (normal range 150–450)	192 ± 91

Note: Values are *n* (%), mean ± SD.
Abbreviations: Alk Phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, g-glutamyltransferase; INR international normalized ratio; SD, Standard deviation.
[a]See Supporting Information S1: Table S1: oxaliplatin (*n* = 13), azathioprine (*n* = 7), methotrexate (*n* = 4), immunosuppressive drugs for liver transplantation (*n* = 11), immunosuppressive drugs for kidney transplantation (*n* = 2), immunosuppressive drugs for combined liver–kidney transplantation (*n* = 1), antineoplastic drugs for extra-hepatic cancers (*n* = 8).
[b]Immunological disorders included hypogammaglobulinemia (*n* = 2), Wegener disease (*n* = 1), and primary biliary cholangitis (*n* = 1).
[c]Genetic disorder included cystic fibrosis (*n* = 2).
[d]Cardiovascular disease included congestive heart failure (*n* = 4) and congenital heart defect (*n* = 1).
[e]Hemocoagulative disorder included multiple myeloma (*n* = 1), myelofibrosis (*n* = 1), polycythemia vera (*n* = 1), and factor V Leiden mutation (*n* = 1).
[f]Data available in 44 patients.
[g]Data available in 18 patients.
[h]Data available in 81 patients.
[i]Data available in 78 patients.
[j]Data available in 80 patients.

liver biopsy in one patient. In 18 patients (22%), a liver resection was performed. The mean biopsy size was 29 ± 13 mm and the mean number of portal tracts was 22 ± 13. Among the 82 liver specimens, 74 (90%) did not have significant fibrosis. Interestingly, no specimen showed other specific signs of PSVD (obliterative portal venopathy or incomplete septal fibrosis). However, non-specific signs of PSVD were frequently associated with NRH in our series, architectural disturbance was the most frequent associated lesion and was present in 77 patients (94%). NRH grades according to the Wanless scoring system are shown in Figure 2.

3.3 | Occurrence of Liver-Related Complications and Mortality

The median length of follow-up was 35.9 months (range 1–83 months). Nine patients were lost to follow-up. Globally,

TABLE 2 | Histological characteristics in 82 patients with NRH.

Indication for liver tissue	
Signs of portal hypertension[a], *n* (%)	29 (35%)
Abnormal liver tests, *n* (%)	20 (24%)
Liver resection for metastasis/cancer, *n* (%)	16 (19%)
Protocol biopsy after liver transplantation, *n* (%)	11 (13%)
Other, *n* (%)	6 (7%)
How liver tissue was obtained	
Percutaneous liver biopsy[b], *n* (%)	17 (21%)
Transjugular liver biopsy, *n* (%)	46 (56%)
Intraoperative liver biopsy, *n* (%)	1 (1%)
Liver resection specimen, *n* (%)	18 (22%)
Histological features	
Mean size[c] + SD (mm)	29 ± 13
Mean number of portal tracts[c] + SD	22 ± 13
Fibrosis (METAVIR > F1), *n* (%)	8 (10%)
NRH Grade 1[d], *n* (%)	27 (33%)
NRH Grade 2[e], *n* (%)	49 (60%)
NRH Grade 3[f], *n* (%)	6 (7%)
Obliterative portal venopaty, *n*	0
Incomplete septal fibrosis, *n*	0
Portal tract abnormalities[g], *n* (%)	62 (76%)
Architectural disturbance[h], *n* (%)	77 (94%)
Non-zonal sinusoidal dilatation, *n* (%)	41 (50%)
Mild perisinusoidal fibrosis, *n* (%)	13 (16%)
Absence of SOS, *n*	78 (95%)
Mild SOS[i], *n* (%)	0
Moderate SOS[j], *n* (%)	3 (4%)
Severe SOS[k], *n* (%)	1 (1%)

Note: Values are *n* (%).
[a]Specific signs of portal hypertension (esophageal varices, portal hypertensive bleeding, portosystemic collaterals at imaging) and nonspecific signs of portal hypertension (ascites, thrombocytopenia, splenomegaly).
[b]Other indications for liver tissue included liver resection for hepatocellular adenoma ($n = 1$), liver biopsy for non-cirrhotic HCC ($n = 1$), dysmorphic liver on imaging ($n = 2$), portal vein thrombosis without signs of portal hypertension ($n = 1$), and liver lesion ($n = 1$).
[c]Surgical resections not included.
[d]Nodules present on reticulin staining but indistinct.
[e]Nodules present on reticulin staining but only occasionally distinct.
[f]Nodules distinctly visible on H&E.
[g]Multiplication, increased number of arteries, periportal vascular channels, aberrant vessels.
[h]Irregular distribution of the portal tracts and central veins.
[i]Centrilobular involvement limited to one-third of the lobular surface.
[j]Centrilobular involvement in two-thirds of the lobular surface.
[k]Complete centrilobular involvement.

17 patients (21%) experienced new liver-related complications during follow-up. All of them had at least one sign of portal hypertension at NRH diagnosis. Five patients (6%) had new-onset ascites, three patients (4%) had variceal bleeding, three patients (4%) had hepatic encephalopathy, four patients (5%) had portal vein thrombosis and two patients (2%) had HCC (Table 3).

Adequate information about the cause of death was available for 77 patients (94%). The cumulative 5-year-liver-related mortality was 5% (Figure 3). The cumulative 5-year-non-liver-related mortality was 20% (Figure 4).

3.4 | NRH Diagnosed Incidentally Versus NRH Diagnosed Clinically

In this study, NRH was diagnosed following clinical suspicion in 55 patients, whereas NRH was diagnosed incidentally in 27 patients (see above). We compared the patients according to the circumstances of NRH diagnosis, either clinically or incidentally (Table 4). Both groups were comparable in terms of age and sex at diagnosis, and liver-related mortality. Interestingly, patients with an incidental diagnosis of NRH had more frequently an identified condition associated with NRH. Indeed, 25 patients (93%) had an history of drug exposure compared with 21 patients (38%) in the group of NRH diagnosed clinically ($p < 0.001$). Oxaliplatin was the most frequent drug represented: 12 patients (41%) had a history of oxaliplatin-based chemotherapy in the group of patients diagnosed incidentally compared with one patient (2%) in the group of NRH diagnosed clinically ($p < 0.001$). Conversely, patients diagnosed clinically were more frequently exposed to azathioprine (13% vs. 0%, $p = 0.04$). During follow-up, patients diagnosed incidentally developed less liver-related complications (4% vs. 27%, $p = 0.01$). In contrast, non-liver related death was significantly higher in patients with an incidental diagnosis of NRH than in patients diagnosed clinically (26% vs. 9%, $p = 0.01$). We also looked for possible histological differences between both groups. Remarkably, patients diagnosed clinically were found to have a significantly higher degree of NRH. Their liver slides also showed more frequent sinusoidal ectasia.

3.5 | Literature Review

The research strategy is detailed in Supporting Information S1. Of 1198 identified records, a total of 10 case series of NRH were selected because of a similar methodology. Their population characteristics are shown in Table 5.

4 | Discussion

In this study, we reported the clinical and histological characteristics and outcome of 82 histology-proven cases of NRH. We compared them with the literature by carrying out a systematic review (see Supporting Information S1) and highlighted the particularities of our series in the hope of contributing to the knowledge of this mysterious entity.

Our series distinguished itself by systematically reporting the indication for liver tissue, the liver-related characteristics at diagnosis and patient outcomes. Moreover, several interesting aspects can be raised.

Besides being the third largest study population in the literature, our series is also interesting in that it recruits NRH cases which

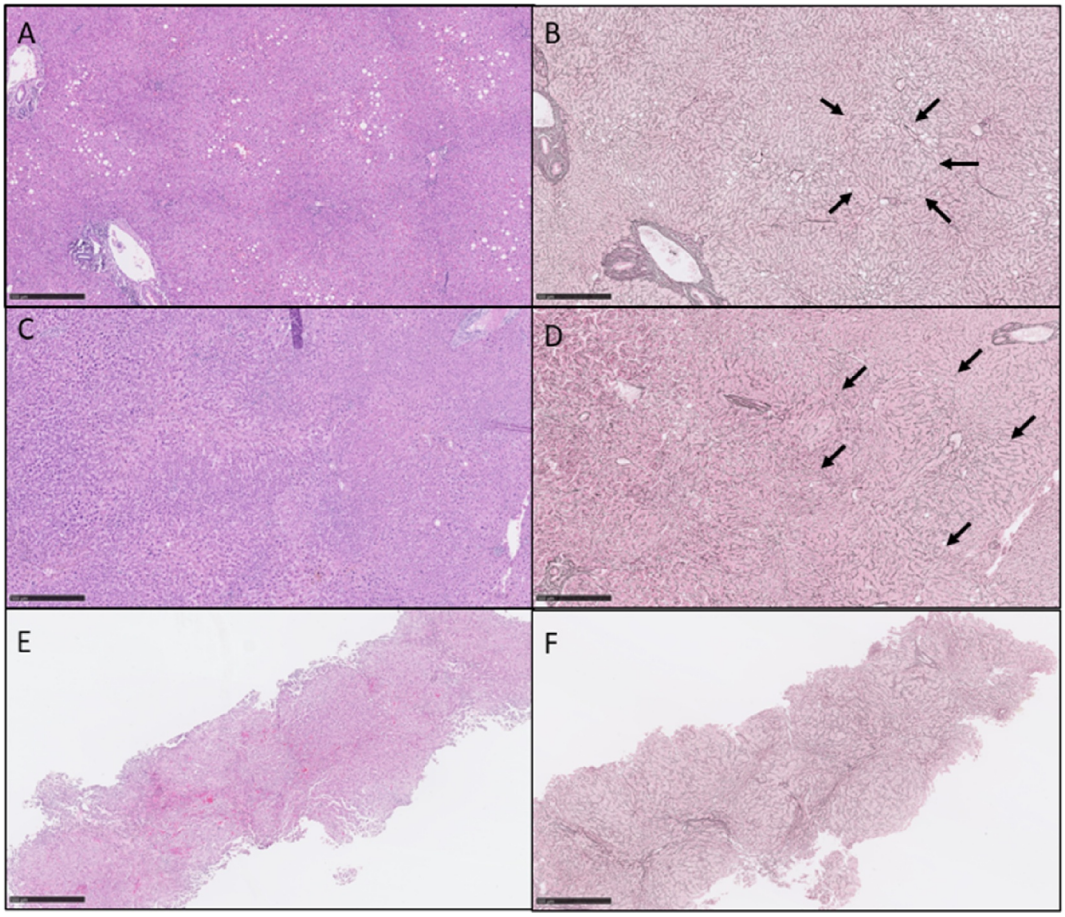

FIGURE 2 | NRH grades according to the Wanless scoring system NRH is graded according to the Wanless scoring system based on the degree of contrast between nodular and internodular tissue. (a and b) NRH Grade 1 shows nodules that are indistinct but occasionally visible with reticulin staining (arrows) (a: H&E 5×, b: reticulin staining 5×). (c and d) NRH Grade 2 shows nodules that are occasionally distinct with H&E staining and more distinct with reticulin staining (c: H&E 5×, d: reticulin staining 5×, arrows show nodules). (e–f) NRH Grade 3 shows distinct nodularity in most areas with both H&E and reticulin staining (e: H&E 5×, f: reticulin staining 5×, arrows show nodules).

TABLE 3 | Liver-related outcomes and mortality in 82 NRH patients.

Complications and medical interventions during follow-up	
Ascites at baseline and during follow-up, *n* (%)	7 (8%)
New onset of ascites[a], *n* (%)	5 (6%)
Variceal bleeding, *n* (%)	3 (4%)
Hepatic encephalopathy, *n* (%)	3 (4%)[a]
Portal vein thrombosis, *n* (%)	4 (5%)
TIPS, *n* (%)	3 (4%)
HCC, *n* (%)	2 (2%)
Liver transplantation[b], *n* (%)	1 (1%)
Liver-related mortality[c], *n* (%)	2 (3%)
Non-liver-related mortality[c], *n* (%)	10 (13%)

[a]One patient who developed hepatic encephalopathy had a TIPS.
[b]Indication for liver transplantation: HCC.
[c]Data available in 77 patients. Causes of liver-related death included sepsis ($n = 1$), spontaneous bacterial peritonitis ($n = 1$).

are both homogeneous and heterogeneous. On the one hand, the recruitment of NRH cases in our study was homogeneous because our study was monocentric, and all liver specimens were reviewed by the same expert liver pathologist (P.B.). This is important because as reported in the literature, the diagnosis of NRH can be challenging due to high interobserver variability [26]. In our study, the histological evaluation could be considered optimal according to the size (mean biopsy size: 29 ± 13 mm), the number of analyzed portal tracts (mean number of portal tracts: 22 ± 13) and the interpretation of our expert liver pathologist. On the other hand, our study comprised a heterogeneous group of NRH cases according to the circumstances of diagnosis, whether clinical or incidental.

The identification of a large group of incidental NRH is the main originality and contribution of our study. In the current study, NRH was diagnosed following clinical suspicion in 55 of the 82 patients (67%), while in 27 patients (33%), NRH was diagnosed completely incidentally following liver resection for metastasis, cholangiocarcinoma, hepatocellular adenoma, or following a protocol biopsy after liver transplantation or a biopsy in a non-cirrhotic HCC. Our study is unique considering the high number of NRHs discovered incidentally. Incidental diagnosis of NRH has rarely been reported in the literature. Indeed, from our literature review, only one case of NRH was diagnosed incidentally during a cholecystectomy [13]. Nevertheless, autopsy series performed more than 30 years ago

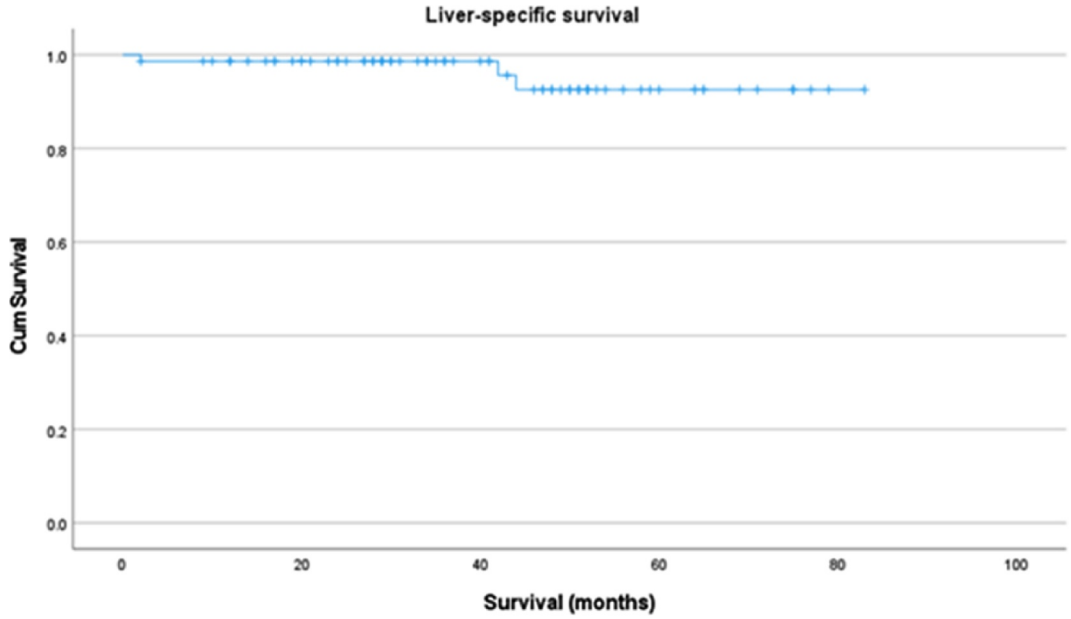

FIGURE 3 | Liver-related mortality-free survival. Kaplan–Meier survival curve for liver-related mortality free survival.

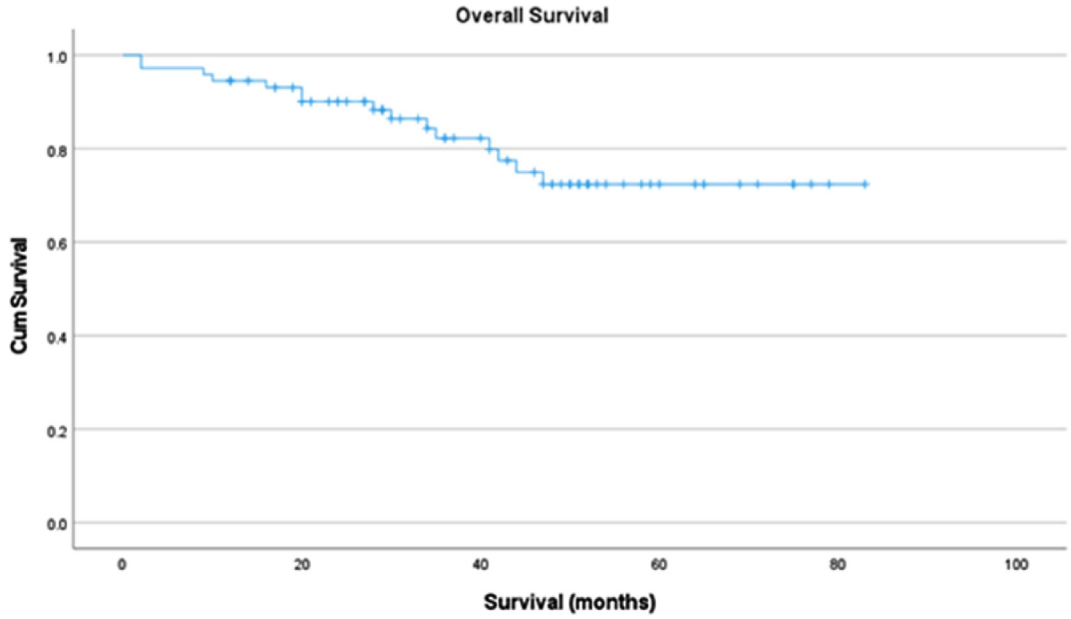

FIGURE 4 | Non-liver-related mortality-free survival. Kaplan–Meier survival curve for non-liver-related mortality free survival.

showed that NRH was an underreported entity that could be present without any clinical manifestations. Indeed, Wanless reviewed the hepatic histology of 2500 consecutive autopsies and found the presence of NRH in 2.6% of the cases in which only one patient had esophageal varices before death [5]. Similarly, Nakamuna examined 577 autopsy livers in Japan and found NRH in 2.1% of cases of whom no patient had esophageal varices antemortem [4]. Interestingly, when we compared cases diagnosed following clinical manifestations with cases diagnosed incidentally, we found that patients with an incidental diagnosis of NRH had a lower rate of liver-related complications during follow-up and a higher rate of non-liver-related mortality. Thus, our study supports the findings of the mentioned autopsies series suggesting that NRH is probably an underreported entity that can exist without any clinical manifestation of portal hypertension and whose clinical significance is therefore uncertain.

From a histological point of view, the most interesting contribution of our series is to show that NRH is not usually associated with the two other pivotal lesions reported in PSVD [7–9]. We asked our pathologist to scrupulously look for the presence of obliterative portal venopathy and incomplete septal fibrosis, but these lesions were not identified in our specimens. In the

TABLE 4 | Comparison between NRH diagnosed incidentally and NRH diagnosed clinically.

	NRH diagnosed incidentally[a] N = 27	NRH diagnosed clinically[b] N = 55	p
Clinical characteristics			
Mean age at diagnosis (years ± SD)	63 ± 16	58 ± 13	ns
Sex (men), *n* (%)	14 (52%)	35 (63%)	ns
Conditions associated with NRH, *n* (%)			
Conditions associated with NRH	25 (93%)	36 (66%)	0.008
Immunosuppressive or antineoplastic drug	25 (93%)	21 (38%)	< 0.001
Oxaliplatin	12 (41%)	1 (2%)	< 0.001
Azathioprine	0 (0%)	7 (13%)	0.04
Immunosuppressive drugs for liver transplantation	8 (30%)	3 (5%)	0.002
Antineoplastic drugs for extra-hepatic cancers	3 (10%)	5 (9%)	ns
Liver-related laboratory findings at diagnosis			
Platelets[c] (×109/L) (normal range 150–450)	219 ± 86	179 ± 91	ns
AST (U/L) (normal range 10–40)	112 ± 185	38 ± 29	< 0.001
ALT (U/L) (normal range 10–40)	131 ± 255	40 ± 40	< 0.001
GGT (U/L) (normal value < 60)	105 ± 164	206 ± 280	ns
Alk Phos[c] (U/L) (normal range 40–130)	121 ± 125	191 ± 207	ns
Bilirubin[c] (mg/dL) (normal value < 1.2)	0.6 ± 0.4	0.8 ± 0.5	ns
INR[d] (normal range 0.80–1.20)	1.1 ± 0.1	1.2 ± 0.3	ns
Albumin[e] (mg/dL) (normal range 35–52)	43 ± 5	38 ± 8	ns
Liver related-complications during follow-up[f], *n* (%)	1 (4%)	15 (27%)	0.01
Liver-related mortality[g], *n* (%)	0 (0%)	3 (7%)	ns
Non-liver-related mortality[g], *n* (%)	7 (26%)	5 (9%)	0.04
Histological characteristics			
Grade, *n* (%)			
Grade 1	15 (55%)	12 (22%)	0.002
Grade 2	11 (41%)	38 (69%)	0.01
Grade 3	1 (3%)	5 (10%)	ns
Portal inflammation, *n* (%)	18 (62%)	21 (40%)	0.052
Lobular inflammation, *n* (%)	2 (7%)	4 (7%)	ns
Sinusoidal ectasia, *n* (%)	8 (30%)	34 (62%)	0.006
Centrolobular cholestasis, *n* (%)	2 (7%)	11 (20%)	ns
Metavir F0, *n* (%)	19 (70%)	36 (66%)	ns
Metavir F1, *n* (%)	7 (26%)	12 (22%)	ns
Metavir > F1, *n* (%)	1 (3%)	7 (13%)	ns

Note: Values are *n* (%), mean ± SD. Grade 1: mild nodularity on reticulin staining. Grade 2: moderate nodularity in both H&E and reticulin staining. Grade 3: strong nodularity in both H&E and reticulin staining.

Abbreviations: Alk Phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, g-glutamyltransferase; INR international normalized ratio; ns, not significant.

[a]NRH diagnosed incidentally includes NRH diagnosed after liver resection for metastasis or cancer ($n = 16$), protocol biopsy in liver-transplanted patients ($n = 11$), liver resection for hepatocellular adenoma ($n = 1$), liver biopsy for non-cirrhotic HCC ($n = 1$).

[b]NRH diagnosed clinically includes NRH diagnosed after signs of portal hypertension ($n = 31$), abnormal liver tests ($n = 20$), dysmorphic liver on imaging ($n = 2$), liver lesion ($n = 1$), portal vein thrombosis without signs of portal hypertension ($n = 1$).

[c]Data available in 81 patients.

[d]Data available in 80 patients.

[e]Data available in 78 patients.

[f]Data available for 78 patients.

[g]Data available for 73 patients.

TABLE 5 | Summary of the 10 included studies.

References	Country	Study period	Number of patients	Indication for liver tissue	Men	Age at diagnosis	Any signs of portal hypertension at diagnosis	Gastro-esophageal varices at diagnosis	Abnormal liver test at diagnosis	Outcome	Comments
Penrice et al. [14]	USA	2002–2017	167	NA	54%	53 ± 16 (mean + standard deviation)	44%	23%	NA	PHT-related complication: 28% at 10 years Transplant-free survival: 30% at 10 years Median time of follow-up: 55 months (range 1–306 months)	The study excluded patients with metastatic liver disease and history of liver transplantation
Navale and Gonzalez [19]	USA	2003–2019	60	Signs of PHT (43%) Malignancy (23%) Abnormal liver tests (12%)	53%	54 years (21–80) (median, range)	47%	NA	NA	NA	
Bakshi et al. [20]	India	2011–2016	22	Signs of PHT (% NA) abnormal liver tests (12%)	55%	40 (16–59) (median, range)	86%	NA	NA	NA	
Guilbert et al. [21]	Canada	1993–2013	26	NA	73%	55 (50–59) (median, interquartile range)	73%	NA	50%	NA	
Barge et al. [22]	France	2007–2014	159	Abnormal liver tests (74%)	52%	54 years (16–91) (mean)	38%	15%	82%	NA	
Rothweiler et al. [23]	Switzerland	1996–2011	51	Abnormal liver tests (100%)	55%	49.2 (9–75) (mean, range)	17.6%	11%	100%	NA	

(Continues)

TABLE 5 | (Continued)

References	Country	Study period	Number of patients	Indication for liver tissue	Men	Age at diagnosis	Any signs of portal hypertension at diagnosis	Gastro-esophageal varices at diagnosis	Abnormal liver test at diagnosis	Outcome	Comments
Morris et al. [13]	UK	1993–2006	42	Abnormal liver tests (52%) Signs of PHT (17%) Jaundice (10%) Macroscopically abnormal liver during cholecystectomy (one patient)	45%	56 (16–90) (mean, range)	31%	26%	NA	Liver-related death: 2% non-liver-related death: 33% Median time of follow-up: 3.4 years(range 0–13.8)	
Colina et al. [24]	Spain	Over a period of 9 years	24	NA	50%	56.4 ± 22.5 (range 15–87)-	37.5%	17%	87.5%	NA	The study included 7 cases of autopsies
Dachman et al. [25]	USA	1981–1984	21	NA	52%	48 (8–81)	28%	19%	NA	NA	The study included cases of autopsies (number not available)
Stromeyer and Ishak 1981 [15]	USA	Not available	30	NA	50%	52.5 (14–80)	56.6%	13%	NA	Liver-related death: 16%	The study included cases of autopsies (number not available)

Abbreviations: NA, not available; PHT, portal hypertension; UK, United Kingdom; USA, United States of America.

literature, the co-existence of the pivotal PSVD lesions has not been systematically studied. NRH in association with obliterative portal venopathy has been documented [5, 27, 28], however, only one case series from our literature review reported the presence of obliterative portal venopathy in 11% of patients with NRH [22]. Conversely the non-specific histological lesions for PSVD were frequently found in our patients with NRH. Our study suggests that PSVD is an umbrella term that regroups several distinct histological features that do not per se occur together. Also, from a histological point of view, another interesting point was that the histology of NRH differed according to the circumstances of discovery, clinically or incidentally: patients diagnosed clinically had more frequent sinusoidal dilatation. The significance of nonobstructive sinusoidal dilatation is unclear; however, it has been described as a histological feature of portal hypertension [29]. Consequently, the presence of sinusoidal dilatation could provide clinicians with clues to identify patients at risk for portal hypertension-related complications.

Concerning the conditions associated with NRH, our study confirmed published data but also showed some specificities, such as the frequent association with oxaliplatin and liver transplantation. Numerous conditions were associated with NRH [10], which can be classified into five groups (drug/toxine exposure, immunological disorder, hemocoagulative disorder, infectious, and congenital/genetic/familial) [17]. In our series, the main condition associated with NRH (56%) was a treatment with immunosuppressive or antineoplastic drugs, and oxaliplatin was the most frequently associated drug. In fact, 13 patients (28%) had a history of FOLFOX chemotherapy (5-fluorouracil and oxaliplatin) as neoadjuvant therapy for colon cancer (Supporting Information S1: Table S1). Curiously, 12 of the 13 patients treated with oxaliplatin were diagnosed incidentally. In our review of similar studies, oxaliplatin was associated with NRH only in one series (Navale et al., number of patients treated with oxaliplatin unknown [19]). Oxaliplatin has been associated with several liver histological damages, the most prevalent being sinusoidal obstruction syndrome [30]. Therefore, we looked for the presence of SOS in 13 patients with a history of oxaliplatin based-chemotherapy. Only two of them had lesions compatible with SOS. Azathioprine was the second most common drug associated with NRH in seven patients (15%) and was more frequent in patients diagnosed clinically. In our systematic review, 6 series reported patients treated with azathioprine (Morris et al. [13], 7%, Penrice et al. [14], 6%, Stromeyer and Ishak [15] 6%, Navale and Gonzalez [19], 7%, Rothweiler et al. [23], 8%, Colina et al. [24], 4%). Moreover, in our series, 11 patients (24%) had been liver transplanted and were taking immunosuppressive drugs. The liver-transplanted patients were transplanted for various causes, and we did not identify any relationship between the cause of the primary liver disease and the occurrence of post-transplant NRH. NRH after liver transplantation has been reported with an incidence between 1% and 5.1% [31–33]. However, no association between immunosuppressive drugs commonly used after liver transplantation (anticalcineurin or mycophenolate mofetil) has been previously described [34]. Blood flow abnormalities occurring after liver transplantation have been suggested as a possible pathophysiological mechanism for the development of NRH [31, 32]. As in our series, all drugs associated with NRH were immunosuppressive drugs, we hypothesize that an immunosuppressive status might be the common denominator in the etiology of NRH in addition to the well-known drug toxicity.

The outcome of our NRH population did not differ from the one reported in the literature (Table 5). The survival at 5 years without clinical complications of portal hypertension was 90% (Supporting Information S1: Figure S2), the liver-related mortality at 5 years was 5% and the non-liver-related mortality at 5 years was 20%. In our systematic review, a prior series found a liver-related death of 2% [13], a non-liver-related death of 33% [13] and a portal hypertension-related complications at 10 years of 28% [14]. Thus, portal hypertension-related complications do not commonly occur and the mortality of NRH patients is mainly driven by the comorbidities of these patients [13–15]. During follow-up, 2 patients developed HCC. The association between NRH and HCC is controversial and has only been reported in case reports [35, 36].

Our study has some limitations. The first limitation concerns the enrollment of patients. Our cohort is monocentric, and our institution is an academic hospital where hepatic surgery (involving transplantation and resection) is performed. Some patients are also referred for complex cases and for procedures such as hepatic venous gradient measurement and TIPS. Consequently, our population may not represent the usual spectrum of NRH. Moreover, the clinical context leading to the liver histological assessment was heterogeneous, including protocol biopsy after liver transplantation and liver histology at the time of hepatic tumor resection. Again, these conditions do not represent the usual spectrum of NRH. Nevertheless, this is, to our opinion, the main interest of our study. Indeed, it allows us to identify a group of incidental NRHs, a pattern of the disease largely unknown in the literature, and to compare them with NRHs diagnosed following clinical suspicion. A second limitation of our study is inherent to the difficulty in diagnosing NRH at histology. The histologic abnormalities of the liver may be subtle, leading to interoperator dependency and consequently some cases may have been missed. A third limitation is the retrospective design of our study. Some interesting data were missing such a detailed work-up at diagnosis (for instance, a screening for coagulopathies was not systematically performed) and a complete follow-up of patients. Finally, we decided to exclude patients who underwent liver resection for colorectal metastases or liver transplantation (see above) from our systematic review. This may impact the generalizability of our study.

In conclusion, the large number of NRH cases observed in our institution confirms the crucial role of the liver pathologist to identify NRH. The diagnosis of NRH requires reticulin staining in specific scenarios, namely in case of abnormal liver tests, unexplained features of portal hypertension, in patients with a history of oxaliplatin-based chemotherapy or in patients who had a liver transplantation. In addition to being the third largest case series of NRH, our study is the first to include NRH cases diagnosed incidentally. Our incidental cases of NRH showed that NRH occurred mainly in the setting of liver transplantation or liver resection for metastasis without signs of portal hypertension at diagnosis and during follow-up. This suggests that NRH could be in some cases just an epiphenomenon and not a

real clinical entity. The natural history of this form of NRH remains up to now totally unknown. Further studies are required to characterize the natural history of NRH not revealed by clinical and/or biological liver signs and to determine whether the clinical phenotype could be related to the condition associated with NRH.

Acknowledgments

The authors thank Dr Colin Dumont for assistance in data acquisition.

Ethics Statement

This study was approved by the ethics committee of Cliniques universitaires Saint-Luc (2021/26AVR/194).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. P. E. Steiner, "Nodular Regenerative Hyperplasia of the Liver," *American Journal Of Pathology* 35 (1959): 943–953.

2. S. Ranstrom, "Miliary Hepatocellular Adenomatosis," *Acta Pathologica et Microbiologica Scandinavica* 33 (1953): 225–229.

3. P. Rougier, C. Degott, B. Rueff, and J. P. Benhamou, "Nodular Regenerative Hyperplasia of the Liver. Report of Six Cases and Review of the Literature," *Gastroenterology* 75, no. 2 (1978): 169–172, https://doi.org/10.1016/0016-5085(78)90396-7.

4. Y. Nakanuma, "Nodular Regenerative Hyperplasia of the Liver: Retrospective Survey in Autopsy Series," *Journal of Clinical Gastroenterology* 12, no. 4 (1990): 460–465, https://doi.org/10.1097/00004836-199008000-00023.

5. I. R. Wanless, "Micronodular Transformation (Nodular Regenerative Hyperplasia) of the Liver: A Report of 64 Cases Among 2,500 Autopsies and a New Classification of Benign Hepatocellular Nodules," *Hepatology* 11, no. 5 (1990): 787–797, https://doi.org/10.1002/hep.1840110512.

6. J. N. L. Schouten, J. Verheij, and S. Seijo, "Idiopathic Non-Cirrhotic Portal Hypertension: A Review," *Orphanet Journal of Rare Diseases* 10, no. 1 (2015): 67, https://doi.org/10.1186/s13023-015-0288-8.

7. A. De Gottardi, P. E. Rautou, J. Schouten, et al., "Porto-Sinusoidal Vascular Disease: Proposal and Description of a Novel Entity," *Lancet Gastroenterol Hepatol* 4, no. 5 (2019): 399–411, https://doi.org/10.1016/s2468-1253(19)30047-0.

8. A. De Gottardi, C. Sempoux, and A. Annalisa Berzigotti, "Porto-Sinusoidal Vascular Disorder," *Journal of Hepatology* 77, no. 4 (2022): 1124–1135, https://doi.org/10.1016/j.jhep.2022.05.033.

9. R. de Franchis, J. Bosch, G. Garcia-Tsao, et al., "Baveno VII – Renewing Consensus in Portal Hypertension," *Journal of Hepatology* 76, no. 4 (2022): 959–974, https://doi.org/10.1016/j.jhep.2021.12.022.

10. M. Hartleb, K. Gutkowski, and P. Milkiewicz, "Nodular Regenerative Hyperplasia: Evolving Concepts on Underdiagnosed Cause of Portal Hypertension," *World Journal of Gastroenterology* 17 (2011): 1400–1409.

11. P. A. Reshamwala, D. E. Kleiner, and T. Heller, "Nodular Regenerative Hyperplasia: Not All Nodules Are Created Equal," *Hepatology* 44, no. 1 (2006): 7–14, https://doi.org/10.1002/hep.21258.

12. A. H. Naber, U. Van Haelst, and S. H. Yap, "Nodular Regenerative Hyperplasia of the Liver: An Important Cause of Portal Hypertension in Non-Cirrhotic Patients," *Journal of Hepatology* 12, no. 1 (1991): 94–99, https://doi.org/10.1016/0168-8278(91)90916-y.

13. J. M. Morris, K. A. Oien, M. McMahon, et al., "Nodular Regenerative Hyperplasia of the Liver: Survival and Associated Features in a UK Case Series," *European Journal of Gastroenterology and Hepatology* 22, no. 8 (2010): 1001–1005, https://doi.org/10.1097/meg.0b013e3283360021.

14. D. D. Penrice, N. Thakral, C. A. Kezer, et al., "Outcomes of Idiopathic Versus Secondary Nodular Regenerative Hyperplasia of the Liver: A Longitudinal Study of 167 Cases," *Liver International* 42, no. 6 (2022): 1379–1385, https://doi.org/10.1111/liv.15202.

15. F. W. Stromeyer and K. G. Ishak, "Nodular Transformation (Nodular 'Regenerative' Hyperplasia) of the Liver. A Clinicopathologic Study of 30 Cases," *Human Pathology* 12, no. 1 (1981): 60–71, https://doi.org/10.1016/s0046-8177(81)80242-0.

16. C. Venturi, C. Sempoux, J. Bueno, et al., "Novel Histologic Scoring System for Long-Term Allograft Fibrosis After Liver Transplantation in Children," *American Journal of Transplantation* 12, no. 11 (2012): 2986–2996, https://doi.org/10.1111/j.1600-6143.2012.04210.x.

17. D. Valla, J. C. Garcia-Pagan, A. De Gottardi, and P. E. Rautou, "Vascular Disorders of the Liver," *VALDIG's Guide to Management and Causes* (Cham, Switzerland: Springer, 2022), 127–129.

18. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *BMJ* 372 (2021): n71, https://doi.org/10.1136/bmj.n71.

19. S. Navale and R. S. Gonzalez, "Mild Changes of Hepatic Nodular Regenerative Hyperplasia May Cause Portal Hypertension and Be Visible on Reticulin but Not Hematoxylin and Eosin Staining," *Virchows Archiv* 479, no. 6 (2021): 1145–1152, https://doi.org/10.1007/s00428-021-03195-2.

20. N. Bakshi, N. Gulati, A. Rastogi, A. Chougule, C. Bihari, and A. Jindal, "Nodular Regenerative Hyperplasia—An Under-Recognized Vascular Disorder of Liver," *Pathology, Research & Practice* 216, no. 4 (2020): 152833, https://doi.org/10.1016/j.prp.2020.152833.

21. M. C. Guilbert, A. Therrien, G. Soucy, D. Trudel, and B. N. Nguyen, "Nodular Regenerative Hyperplasia: Expression Pattern of Glutamine Synthetase and a Potential Role for Hepatic Progenitor Cells," *Applied Immunohistochemistry & Molecular Morphology* 28, no. 3 (2020): 243–248, https://doi.org/10.1097/pai.0000000000000793.

22. S. Barge, V. Grando, J. C. Nault, et al., "Prevalence and Clinical Significance of Nodular Regenerative Hyperplasia in Liver Biopsies," *Liver International* 36, no. 7 (2016): 1059–1066, https://doi.org/10.1111/liv.12974.

23. S. Rothweiler, L. Terracciano, L. Tornillo, M. T. Dill, M. H. Heim, and D. Semela, "Downregulation of the Endothelial Genes Notch1 and ephrinB2 in Patients With Nodular Regenerative Hyperplasia," *Liver International* 34, no. 4 (2014): 594–603, https://doi.org/10.1111/liv.12261.

24. F. Colina, N. Alberti, A. J Solis, and F. J. Martinez-Tello, "Diffuse Nodular Regenerative Hyperplasia of the Liver (DNRH). A Clinicopathologic Study of 24 Cases," *Liver* 9, no. 5 (1989): 253–265, https://doi.org/10.1111/j.1600-0676.1989.tb00409.x.

25. A. H. Dachman, P. R. Ros, Z. D. Goodman, W. W. Olmsted, and K. G. Ishak, "Nodular Regenerative Hyperplasia of the Liver: Clinical and Radiologic Observations," *American Journal of Roentgenology* 148, no. 4 (1987): 717–722, https://doi.org/10.2214/ajr.148.4.717.

26. B. Jharap, D. P. van Asseldonk, N. K. H. de Boer, et al., "Diagnosing Nodular Regenerative Hyperplasia of the Liver Is Thwarted by Low Interobserver Agreement," *PLoS One* 10, no. 6 (2015): e0120299, https://doi.org/10.1371/journal.pone.0120299.

27. D. Cazals-Hatem, S. Hillaire, M. Rudler, et al., "Obliterative Portal Venopathy: Portal Hypertension is Not Always Present at Diagnosis,"

Journal of Hepatology 54, no. 3 (2011): 455–461, https://doi.org/10.1016/j.jhep.2010.07.038.

28. M. Guido, S. Sarcognato, A. Sonzogni, et al., "Obliterative Portal Venopathy Without Portal Hypertension: An Underestimated Condition," *Liver International* 36, no. 3 (2016): 454–460, https://doi.org/10.1111/liv.12936.

29. C. Marzano, D. Cazals-Hatem, P. E. Rautou, and D. C. Valla, "The Significance of Nonobstructive Sinusoidal Dilatation of the Liver: Impaired Portal Perfusion or Inflammatory Reaction Syndrome," *Hepatology* 62, no. 3 (2015): 956–963, https://doi.org/10.1002/hep.27747.

30. L. Rubbia-Brandt, G. Y. Lauwers, H. Wang, et al., "Sinusoidal Obstruction Syndrome and Nodular Regenerative Hyperplasia Are Frequent Oxaliplatin-Associated Liver Lesions and Partially Prevented by Bevacizumab in Patients With Hepatic Colorectal Metastasis," *Histopathology* 56, no. 4 (2010): 430–439, https://doi.org/10.1111/j.1365-2559.2010.03511.x.

31. H. Devarbhavi, S. Abraham, and P. S. Kamath, "Significance of Nodular Regenerative Hyperplasia Occurring De Novo Following Liver Transplantation," *Liver Transplantation* 13, no. 11 (2007): 1552–1556, https://doi.org/10.1002/lt.21142.

32. A. K. Chen, T. Lunow-Luke, S. Yamaguchi, et al., "Nodular Regenerative Hyperplasia After Liver Transplant; It's All in the Presentation," *Front Surg* 9 (May 2022): 876818, https://doi.org/10.3389/fsurg.2022.876818.

33. I. Kounis, M. Sebagh, M. Evain, et al., "Nodular Regenerative Hyperplasia Is Not a Rare Condition after Liver Transplantation: Incidence, Predictive Factors, and Impact on Survival," *Transplantation* 107, no. 2 (2023): 410–419, https://doi.org/10.1097/tp.0000000000004303.

34. C. Piao, A. Koul, D. Gui, L.-X. Chen, and S. Sarkar, "Noncirrhotic Portal Hypertension Secondary to Nodular Regenerative Hyperplasia Postrenal Transplant," *ACG Case Rep J* 6, no. 12 (2019): e00257, https://doi.org/10.14309/crj.0000000000000257.

35. U. C. Nzeako, Z. D. Goodman, and K. G. Ishak, "Hepatocellular Carcinoma and Nodular Regenerative Hyperplasia: Possible Pathogenetic Relationship," *American Journal of Gastroenterology* 91 (1996): 879–884.

36. S. Kobayashi, K. Saito, and Y. Nakanuma, "Nodular Regenerative Hyperplasia of the Liver in Hepatocellular Carcinoma. An Autopsy Study," *Journal of Clinical Gastroenterology* 16, no. 2 (1993): 155–159, https://doi.org/10.1097/00004836-199303000-00016.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.