VILNIUS UNIVERSITY

FACULTY OF MEDICINE

Thesis work

Extrarenal Manifestations and Long-term Kidney Outcomes of HNF1-beta Nephropathy in Children: Systemic Review

HNF1-beta nefropatijos ekstrarenalinė išraiška vaikystėje ir ilgalaikės inkstų išeitys: sisteminė literatūros apžvalga

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2024-05-10

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SUMMARY

Adult manifestations of HNF1B deficiency are increasingly recognized, yet a comprehensive assessment of the phenotype and long-term kidney outcomes in HNF1B nephropathy across childhood and adulthood remains elusive. This systematic literature review aims to delineate the longitudinal trajectory of kidney function, kidney – associated complications, and extrarenal manifestations in genetically confirmed HNF1B nephropathy cases across pediatric and adult populations, offering practical recommendations for clinicians. Scientific publications were screened in PubMed/Medline database, resulting in 91 included studies with 528 eligible patients. Only full-text clinical case reports and case series with sufficient patient-level data were included for aggregated analysis. Of the patients, 52% presented with de novo HNF1B mutations and 48% with inherited mutations, with whole HNF1B gene deletion being the most prevalent mutation category up to age 50. Furthermore, a tendency for kidney function deterioration was observed, with an average yearly estimated glomerular filtration rate decline of -2.56 ml/min/1.73m². Linear regression analysis identified older age and higher estimated glomerular filtration rate at diagnosis as statistically significant predictors of estimated glomerular filtration rate change. Kaplan-Meier survival curve modeling revealed that by age 29, 10% of patients had reached chronic kidney disease stage 5, increasing to 40% by age 58, indicating a higher risk of progression to end-stage kidney disease. Prenatally, hyperechogenic kidneys were most prevalent (62%), while kidney cysts were more frequent at diagnosis (68%) and last follow-up (73%). Notably, proteinuria incidence (39%) exceeded hypertension (16%), and hyperuricemia emerged as the most prevalent extrarenal manifestation (41%), followed by diabetes (39%) and hypomagnesemia (32%). Proteinuria and hypomagnesemia were most common in the partial HNF1B gene deletion group ($P = 0.008$ and $P = 0.006$, respectively), while hyperuricemia predominated in the splice site mutation group ($P = 0.002$). 163 patients had diabetes, with a median onset age of 22 years (interquartile range: 19.5 years), spanning from 1 to 65 years, and occurring in 50% of cases by age 22. Clinicians should suspect HNF1B-associated disease in patients presenting with hyperechogenic kidneys and kidney cysts, particularly in those with concurrent diabetes, hyperuricemia or hypomagnesemia, even without a positive family history. These findings underscore the importance of regular kidney function monitoring and consideration of mutation type in patient management.

Keywords: HNF1B nephropathy, HNF1B-associated disease, pediatrics, extrarenal manifestations, long-term kidney outcomes.

SANTRAUKA

Dažnėjant HNF1B geno mutacijų nustatymui suaugusiesiems vis dar trūksta išsamaus HNF1B nefropatijos fenotipo ir ilgalaikių inkstų išeičių įvertinimo vaikystėje ir suaugusiųjų amžiuje. Šios sisteminės literatūros apžvalgos tikslas - nustatyti ilgalaikes inkstų funkcijos, inkstų ir ekstrarenalinių ligos manifestacijų tendencijas genetiškai patvirtinta HNF1B nefropatija sergančių vaikų ir suaugusiųjų populiacijose ir pateikti praktinių rekomendacijų gydytojams. Naudojantis PubMed/Medline duomenų baze į šią apžvalgą įtrauktas 91 tyrimas ir atrinkti 528 pacientai. Apibendrintai analizei buvo vertinami tik viso teksto prieigos klinikinių atvejų aprašymai ir atvejų serijos su pakankamu pacientų duomenų kiekiu. Iš viso 52 % pacientų buvo nustatytos de novo HNF1B mutacijos, o 48 % - paveldėtos mutacijos, ir iki 50 metų amžiaus labiausiai paplitusi HNF1B geno mutacijų kategorija buvo viso geno delecija. Be to, buvo pastebėta HNF1B nefropatija sergančių pacientų inkstų funkcijos blogėjimo tendencija: vidutinis metinis apskaičiuotas glomerulų filtracijos greičio sumažėjimas buvo -2,56 ml/min/1,73m². Atlikus tiesinę regresinę analizę nustatyta, kad vyresnis amžius ir didesnis glomerulų filtracijos greičio rodmuo diagnozės nustatymo metu yra statistiškai reikšmingi glomerulų filtracijos greičio pokyčius prognozuojantys veiksniai. Kaplano-Meierio išgyvenamumo kreivės duomenimis 10% pacientų iki 29 metų pasiekė 5 lėtinės inkstų ligos stadiją, o 58 metų amžiuje šis skaičius padidėjo iki 40 %, atspindint didesnę riziką HNF1B nefropatija sergantiems pacientams pereiti į galutinę inkstų funkcijos nepakankamumo stadiją. Prenataliniu laikotarpiu labiausiai paplitęs inkstų ultragarsinio tyrimo pakitimas buvo hiperechogeniniai inkstai (62 %), o inkstų cistos stebėtos dažniau diagnozės nustatymo metu (68 %) ir paskutinio stebėjimo metu (73 %). Pastebėtina, kad tiriamojoje kohortoje proteinurijos dažnis (39 %) viršijo hipertenzijos paplitimo dažnį (16 %), o hiperurikemija buvo labiausiai paplitusi ekstrarenalinė manifestacija (41 %), po jos sekant diabetui (39 %) ir hipomagnezemijai (32 %). Proteinurija ir hipomagnezemija buvo labiausiai paplitusios dalinės HNF1B geno delecijos grupėje (atitinkamai P = 0.008 ir P = 0.006), o hiperurikemija vyravo HNF1B geno splaisingo vietos mutacijos grupėje (P = 0.002). Iš viso diabetu sirgo 163 pacientai, kurių amžiaus mediana buvo 22 metai (interkvartilinis intervalas - 19,5 metų), apimant diabeto pradžios amžiaus spektrą nuo 1 iki 65 metų. 50 % atvejų diabetas pasireiškė pacientams iki 22 metų amžiaus. Šios apžvalgos duomenimis, gydytojai turėtų įtarti su HNF1B asocijuotą ligą pacientams, kuriems stebimi hiperechogeniniai inkstai ar inkstų cistos, ypač kartu su diabeto, hiperurikemijos ar hipomagnezemijos pasireiškimu, net ir neturint teigiamos šeimos anamnezės. Šios sisteminės apžvalgos rezultatai pabrėžia reguliarios inkstų funkcijos stebėsenos ir atsižvelgimo į HNF1B mutacijos tipą gydant pacientus svarbą.

Raktiniai žodžiai: HNF1B nefropatija, HNF1B asocijuota liga, pediatrija, ekstrarenalinės manifestacijos, ilgalaikės inkstų išeitys.

INTRODUCTION

The hepatocyte nuclear factor-1 beta (HNF1B) gene, situated on chromosome 17q12, encodes the HNF-1ß protein, a member of the hepatocyte nuclear factor family of transcription factors. These factors play pivotal roles in tissue-specific gene regulation across various organs, including the kidneys, liver, biliary ducts, intestine, lungs, pancreas, and the urogenital tract (1,2,3,4). During embryogenesis, HNF1B influences organogenesis, such as ureteric bud branching during nephrogenesis, leading to cystic disease in HNF1B-associated pathologies (5,6). Additionally, HNF1B regulates gene expression involved in cell cycle regulation and apoptosis, implicating its relevance in neoplastic conditions. Dysregulation of HNF1B is evident in various cancers, including hepatocellular, kidney, colorectal, endometrial, prostate, and ovarian cancers (3,7).

HNF1B mutations, comprising around half of cases, frequently manifest as heterozygous whole-gene deletions within the 17q12 chromosomal microdeletion context, encompassing 14 other genes across at least 1.4 Mb (4,6). In the remaining cases, heterozygous intragenic point mutations predominate (3,4). Over 230 HNF1B allelic variants associated with disease have been reported, and these variants often cluster in the first 4 exons of the gene, with hotspots observed in exons 2 and 4, as well as the intron 2 splice site (6). Notably, de novo mutations contribute to up to 50% of cases, complicating familial identification (4,6).

Heterozygous HNF1B mutations characterize HNF1B-associated disease, a dominantly inherited clinical entity with a variable multisystem phenotype (1,3,5,8). Extrarenal manifestations include early-onset diabetes mellitus (maturity-onset diabetes of the young type 5), genital tract malformations, abnormal liver function test results, pancreatic hypoplasia, and electrolyte abnormalities, such as hypomagnesemia and hyperuricemia (5). However, neurological and psychiatric manifestations, such as mild cognitive impairment, autism, schizophrenia, and structural brain alterations, often coincide with 17q12 microdeletion rather than HNF1B mutations directly (5,6).

Kidney involvement emerges as the earliest and most prevalent feature of HNF1B-associated disease, spanning from tubular transport abnormalities to structural malformations like duplex or horseshoe kidneys (3). Prenatally, the presentation frequently comprises bilateral hyperechogenic kidneys with or without cortical cysts, while bilateral kidney hypodysplasia with few or multiple cysts is more prevalent in early childhood (3). Notably, HNF1B nephropathy may present clinically only in adulthood (3). The

long-term kidney prognosis varies, with up to 40% of patients progressing to kidney impairment, underscoring the importance of longitudinal monitoring (4,9).

Challenges in diagnosing HNF1B-associated disease persist due to phenotypic variation complexity, frequent de novo mutations, intrafamilial variability, and phenocopies within families (3). The absence of clear genotype-phenotype correlations underscores the multifaceted nature of HNF1B-associated disease, likely stemming from haploinsufficiency (4,6). Additionally, while pediatric populations have received more attention, increasing recognition of adult-onset manifestations necessitates a nuanced understanding of the phenotype and long-term kidney outcomes, which remains lacking (3,6).

This systematic literature review aims to delineate the longitudinal kidney function trajectory, kidney – associated complications, and extrarenal manifestations of genetically confirmed HNF1B nephropathy in both pediatric and adult populations, offering practical recommendations for clinicians.

The main objectives of this review are:

1. To analyze the prevalence of four HNF1B mutation types (whole HNF1B gene deletions, partial HNF1B gene deletions, HNF1B missense mutations, and HNF1B splice site mutations) across different age groups and mutation inheritance patterns in HNF1B nephropathy patients;

2. To investigate long-term kidney function outcomes and possible associations between kidney function and specific HNF1B mutation types;

3. To analyze the kidney ultrasound features observed in HNF1B nephropathy patients prenatally, at the time of diagnosis and at last follow-up;

4. To examine the frequency and genotype – phenotype correlations of kidney - associated complications (such as hypertension and proteinuria);

5. To assess the prevalence and genotype – phenotype correlations of extrarenal manifestations (including diabetes, hyperuricemia, and hypomagnesemia).

METHODOLOGY

The systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (10).

Inclusion criteria:

1. Scientific articles with full-text availability.
2. Studies involving human participants.
3. Clinical case reports and case series with patient-level data provided.
4. Studies analyzing both children and adults with genetically confirmed HNF1B nephropathy.
5. Studies examining kidney and extrarenal manifestations of HNF1B nephropathy in children and/or adults.
6. Studies investigating long-term kidney outcomes of HNF1B nephropathy in children and/or adults.

Exclusion criteria:

1. Articles without full-text access.
2. In vitro, cell, and animal studies.
3. Articles categorized as experimental research, expert consensus, letters to the editor, editorials, conference abstracts, cross-sectional studies, case-control studies, cohort studies, randomized controlled trials, qualitative studies, meta-analyses, and systematic reviews.

The PubMed online database was utilized for the literature search, conducted between April 23, 2022, and October 21, 2023. The keyword combination employed was: ("Hepatocyte Nuclear Factor 1-beta"[Mesh] OR "HNF1B protein, human" [Supplementary Concept] OR "HNF1beta" OR "HNF-1-beta" OR "HNF1 beta A" OR "HNF-1B" OR "HNF1β" OR "Hepatocyte Nuclear Factor" OR "VHNF1" OR "MODY5" OR "LFB3" OR "TCF2" OR "TCF-2" OR "Homeoprotein LFB3" OR "HNF2" OR "Variant Hepatic Nuclear Factor" OR "Transcription Factor 2, Hepatic" OR "Transcription Factor 2" OR "RCAD" OR "Kidney cysts and diabetes syndrome" OR "17q12 deletion") AND ("Kidney"[Mesh] OR kidney OR kidney).

No active search filters were applied during the literature search in the PubMed database. The selection of articles was performed by a single independent researcher following the established protocol, selection criteria, and keyword combination. After the initial PubMed search, 1020 articles were identified. Duplicate articles were removed using Ryann, an intelligent systematic review application. Titles and

abstracts were screened for compliance with the inclusion criteria, and the full text of selected articles was thoroughly assessed for suitability. A flowchart illustrating all stages of the articles selection process and their outcomes is provided in Figure 1.

All enrolled studies met the following criteria:

1. Confirmation of HNF1B diagnosis through genetic testing.
2. Provision of patient-level data on kidney and extrarenal manifestations or long-term kidney outcomes.
3. Availability of full-text access.

Data extracted from the articles was tabulated and analyzed based on the following clinical, genetic, and laboratory variables:

1. Inheritance pattern of HNF1B mutations.
2. Characteristics of HNF1B mutations.
3. Family history.
4. Prenatal kidney ultrasound findings.
5. Age at diagnosis and last follow-up.
6. Estimated glomerular filtration rate (eGFR) at diagnosis and last follow-up.
7. Chronic kidney disease (CKD) stage at diagnosis and last follow-up.
8. Hypertension status at diagnosis and last follow-up.
9. Proteinuria status at diagnosis and last follow-up.
10. Diabetes status at diagnosis and last follow-up.
11. Hyperuricemia status at diagnosis and last follow-up.
12. Hypomagnesemia status at diagnosis and last follow-up.
13. Kidney ultrasound (US) findings at diagnosis and last follow-up.
14. Fatal outcomes.

The analysis of HNF1B mutation characteristics involved classifying mutations into four main groups: whole HNF1B gene deletions (n = 155), partial HNF1B gene deletions (n = 93), HNF1B missense mutations (n = 66), and HNF1B splice site mutations (n = 20). Additionally, 17q12 chromosome microdeletions (n = 26) were classified as whole HNF1B gene deletions, and HNF1B nonsense mutations (n = 10) were categorized as partial HNF1B gene deletions.

Estimated GFR was calculated for 67 patients using the MDRD formula, this also included 63 children in whom Schwartz equation could not be used because height was not provided. For the remaining 183 patients eGFR value was provided (by utilizing either MDRD or CKD-EPI calculation). In total, eGFR at the time of HNF1B nephropathy diagnosis was available for 250 patients.

The demographic, clinical, and genetic characteristics of the patients were analyzed using descriptive statistics. Data were presented as medians (95% confidence interval, CI) for continuous variables and as counts (percentages) for categorical variables. Before proceeding to the analysis of differences, Shapiro–Wilk normality tests were performed for continuous variables revealing non-normal distributions. Proportions were compared using either the chi-square test of independence or Fisher's exact test. For non-normally distributed continuous variables, the Kruskal-Wallis test was employed for group comparisons, and the Mann-Whitney U test was used for pairwise comparisons. Post-hoc group comparisons were adjusted using the Bonferroni correction. Correlations between variables were assessed by Spearman rank order correlation. Linear regression models were employed for further examination of the relationships between variables. To illustrate the probability of not developing stages 3, 4, and 5 CKD at specific follow-up ages for patients with HNF1B nephropathy, Kaplan-Meier survival curve models were adapted. All statistical tests were two-sided, with statistical significance set at $P < 0.05$. Statistical analyses and graphical representations were conducted using R Statistical Analysis software, version 4.3.3.

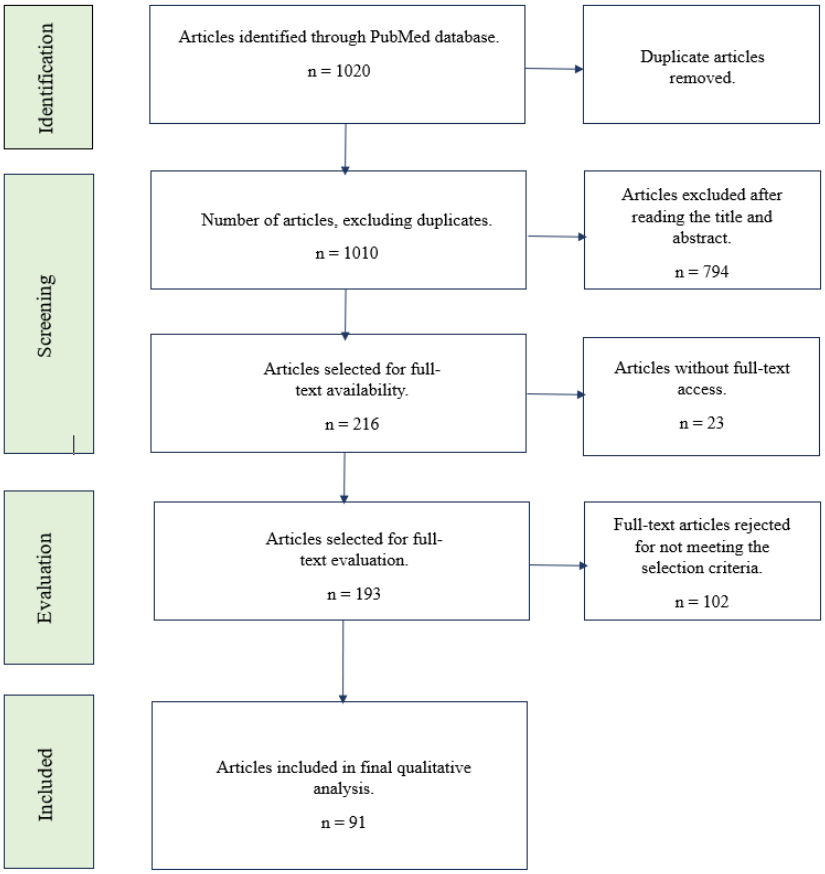

Figure 1. PRISMA Article Selection Strategy Flowchart.

RESULTS

Demographic and Clinical Characteristics

A total of 528 eligible patients from 91 studies were included in this review. A summary of the main demographic, clinical, and genetic data is provided in Table No. 1.

Table No. 1. Summary of Demographic, Clinical, and Genetic Data for HNF1B Nephropathy Patients.

	All patients (n = 528)	Partial HNF1B deletion (n = 103)	Whole HNF1B deletion (n = 181)	HNF1B missense mutation (n = 85)	HNF1B splice site mutation (n = 30)
Age at diagnosis (y) (median, min-max, IQR)	11 (0-78), 27	18 (0-67), 23	6 (0-72), 17	12 (0-65), 28	16.5, (0-65), 27
Sex (M/F) (n, %)	224 (54%) / 189 (46%)	41 (45%) / 51 (55%)	64 (59%) / 45 (41%)	37 (54%) / 32 (46%)	15 (62%) / 9 (38%)
Mutation known (n, %)	510	103 (20%)	181 (35%)	85 (17%)	30 (6%)
CKD stage at diagnosis (n, %): CKD 1 CKD 2 CKD 3 CKD 4 CKD 5	413: 149 (36%); 86 (21%); 116 (28%); 31 (7%); 31 (7%).	97: 21 (22%); 20 (21%); 34 (35%); 10 (10%); 12 (12%).	121: 56 (46%); 25 (21%); 29 (24%); 6 (5%); 5 (4%).	65: 18 (28%); 9 (14%); 22 (34%); 9 (14%); 7 (11%).	26: 9 (35%); 7 (27%); 4 (15%); 3 (11%); 3 (11%).
eGFR at diagnosis (n, %, median): >90 60-89 30-59 15-29 <15	250, 58: 59 (24%), 107; 60 (24%), 69; 100 (40%), 45; 24 (10%), 23; 7 (3%), 11.	75, 54: 13 (17%), 130; 16 (21%), 69; 32 (43%), 47; 10 (13%), 24; 4 (5%), 13.	72, 65: 20 (28%), 98; 21 (29%), 70; 25 (35%), 44; 5 (7%), 23; 1 (1%), 9.	40, 49: 5 (12%), 114; 8 (20%), 67; 21 (52%), 43; 6 (15%), 17; 0 (0%), 0.	15, 61: 4 (27%), 138; 4 (27%), 68; 3 (20%), 44; 3 (20%), 25; 1 (7%), 14.
Patients with follow-up data (n, %)	156	38 (24%)	45 (29%)	25 (16%)	6 (4%)
Follow-up duration (y) (median, min-max, IQR)	3.5 (0.5-33), 7	6.5 (0.1-33), 7	3.4 (0.1-28), 7	3 (0.5-15), 7	3 (1-8), 6
CKD stage at last follow-up (n, %): CKD 1 CKD 2 CKD 3 CKD 4 CKD 5	153: 47 (31%); 28 (18%); 46 (30%); 14 (9%); 18 (12%).	41: 9 (22%); 8 (19%); 11 (27%); 4 (10%); 9 (22%).	40: 19 (47%); 8 (20%); 9 (22%); 2 (5%); 2 (5%).	29: 4 (14%); 6 (21%); 14 (48%); 1 (3%); 4 (14%).	5: 2 (40%); 0 (0%); 2 (40%); 1 (20%); 0 (0%).
eGFR at last follow-up (n, %, median): >90 60-89 30-59 15-29 <15	139, 60: 45 (32%), 95; 26 (19%), 69; 43 (31%), 45; 13 (9%), 23; 12 (9%), 10.	40, 44: 9 (22%), 118; 8 (20%), 69; 11 (27%), 44; 4 (10%), 22; 8 (20%), 11.	36, 73: 16 (44%), 102; 8 (22%), 69; 8 (22%), 48; 2 (6%), 23; 2 (6%), 6.	24, 49: 4 (17%), 93; 5 (21%), 68; 13 (54%), 40; 1 (4%), 23; 1 (4%), 9.	5, 60: 2 (40%), 91; 0 (0%), 0; 2 (40%), 53; 1 (20%), 23; 0 (0%), 0.
Diabetes at diagnosis (n, %)	128	41 (32%)	40 (31%)	25 (19%)	2 (2%)
Hypomagnesemia at diagnosis (n, %)	86	17 (20%)	25 (29%)	5 (6%)	4 (5%)
Hyperuricemia at diagnosis (n, %)	92	22 (24%)	18 (19%)	13 (14%)	12 (13%)
Hypertension at diagnosis (n, %)	17	7 (41%)	3 (18%)	6 (35%)	0 (0%)
Proteinuria at diagnosis (n, %)	45	24 (53%)	4 (9%)	13 (29%)	0 (0%)

Age at the time of HNF1B nephropathy diagnosis was available for 426 patients, with 157 being adults. The median age at diagnosis was 11 years (Interquartile range (IQR): 27 years), ranging from neonates to 78 years old. For patients with available follow-up data (n=156), the median follow-up duration was 3.5 years (IQR: 7 years), ranging from 0.5 to 33 years. Among the 156 patients with available follow-up data, 84 were adults at their last follow-up. The median age of this cohort at the last follow-up was 20 years (IQR: 31 years), with ages ranging from neonates to 77 years old.

In the analyzed cohort, nine patients experienced fatal outcomes, with six deaths attributed to kidney disease. The main demographic, genetic, and clinical characteristics of these patients are summarized in Annex No. 1.

The cumulative incidence of all 426 HNF1B nephropathy diagnosis cases with known age of onset is depicted in Figure 2. The graph illustrates an initial rapid increase in new HNF1B nephropathy cases,

followed by a gradual decline. According to the diagram, 50% of HNF1B nephropathy cases are diagnosed by age 11, and 75% by age 29.

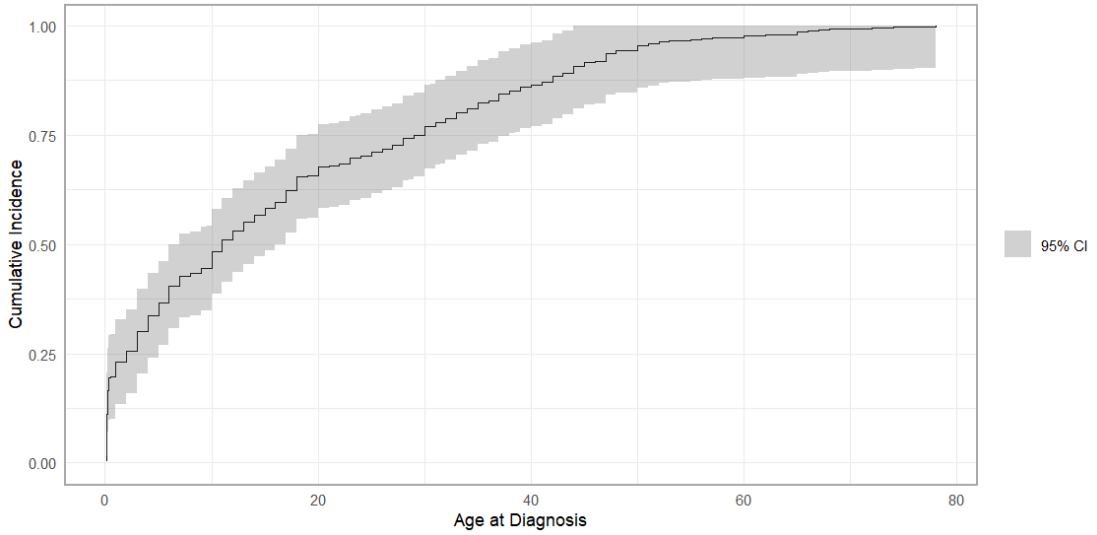

Figure 2. Cumulative Incidence Plot of HNF1B Nephropathy.

Among the 111 patients with family history data, the majority had a family history of kidney disease (n = 46, 41.4%), followed by diabetes (n = 35, 31.53%), and both diseases (n = 28, 25.2%).

Genetic Analysis

Among the 159 patients with reported HNF1B inheritance types, de novo mutations were more common (n = 83, 52%) than paternally or maternally inherited mutations (n = 76, 48%) (Figure 3).

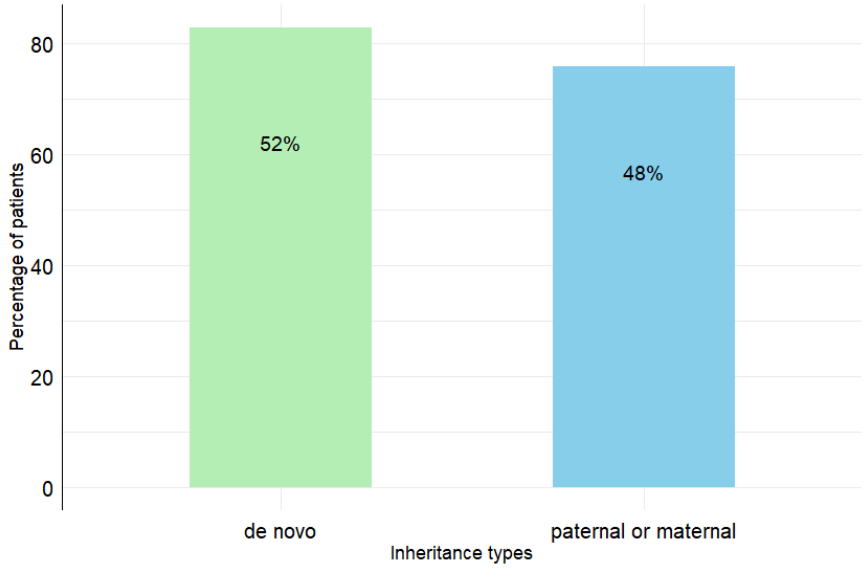

Figure 3. Distribution of HNF1B Mutation Inheritance Types Among Patients.

Of the 510 patients with reported HNF1B mutation type data, 399 were analyzed according to four main mutation categories: 1) whole HNF1B gene deletion (w_deletion, n = 181, 45%); 2) partial HNF1B gene deletion (p_deletion, n = 103, 26%); 3) HNF1B missense mutation (missense, n = 85, 21%); and 4) HNF1B splice site mutation (splice, n = 30, 7.5%). The cumulative incidence of HNF1B nephropathy mutation types is illustrated in Figure 4. Whole HNF1B gene deletion was the most prevalent category across all age groups up to 50 years old. Notably, until approximately 33 years old, the prevalence of whole HNF1B deletions was particularly higher than partial HNF1B deletions, with a ratio of 2.3:1 at 10 years of age, 1.6:1 at 20 years of age and 1.2:1 at 30 years of age. Subsequently, after 33 years of age, the disparity between whole HNF1B deletions and missense / splice site HNF1B mutations became more prominent. Therefore, the prevalence of different ages at the time of HNF1B nephropathy diagnosis varied depending on the specific type of HNF1B mutation.

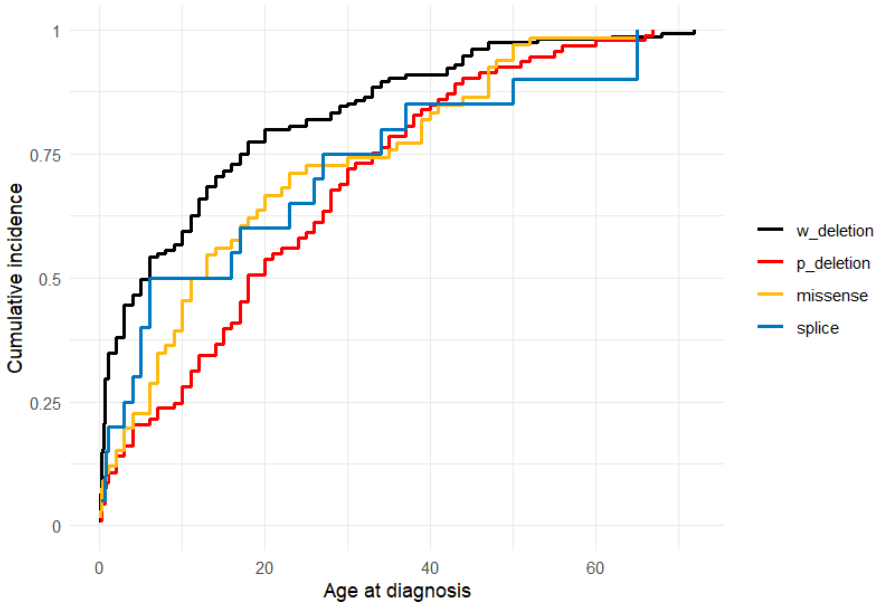

Figure 4. Cumulative Incidence of HNF1B Nephropathy Mutation Categories.

To delineate the age at HNF1B nephropathy diagnosis distribution among different mutation types, violin plots were constructed (Figure 5). Analysis of 399 patients with available data on HNF1B mutation type and age at diagnosis revealed distinct distributions. Notably, the kernel density plot for whole HNF1B gene deletion exhibited the widest base, suggesting a higher probability of diagnosis at a younger age, with a median onset at 6 years. Conversely, patients with HNF1B missense and splice site mutations tended to be diagnosed at older ages, with median onset at 12 and 11 years, respectively. The density curve for HNF1B partial deletions showed a more uniform distribution, with the highest median age at diagnosis observed at 18 years. Statistical analysis using the Kruskal-Wallis test revealed significant variability in age at diagnosis across all mutation types ($P<0.001$). Subsequent pairwise comparisons, employing the Mann – Whitney U test with Bonferroni correction, unveiled non-significant differences ($P\_Bonferroni\ adjusted > 0.05$) in age at diagnosis between partial HNF1B gene deletion and both missense mutation, as well as splice site mutation groups. However, a significant distinction ($P\_Bonferroni\ adjusted = 0.001$) was observed between age at diagnosis in individuals with whole HNF1B gene deletion and those with missense mutations.

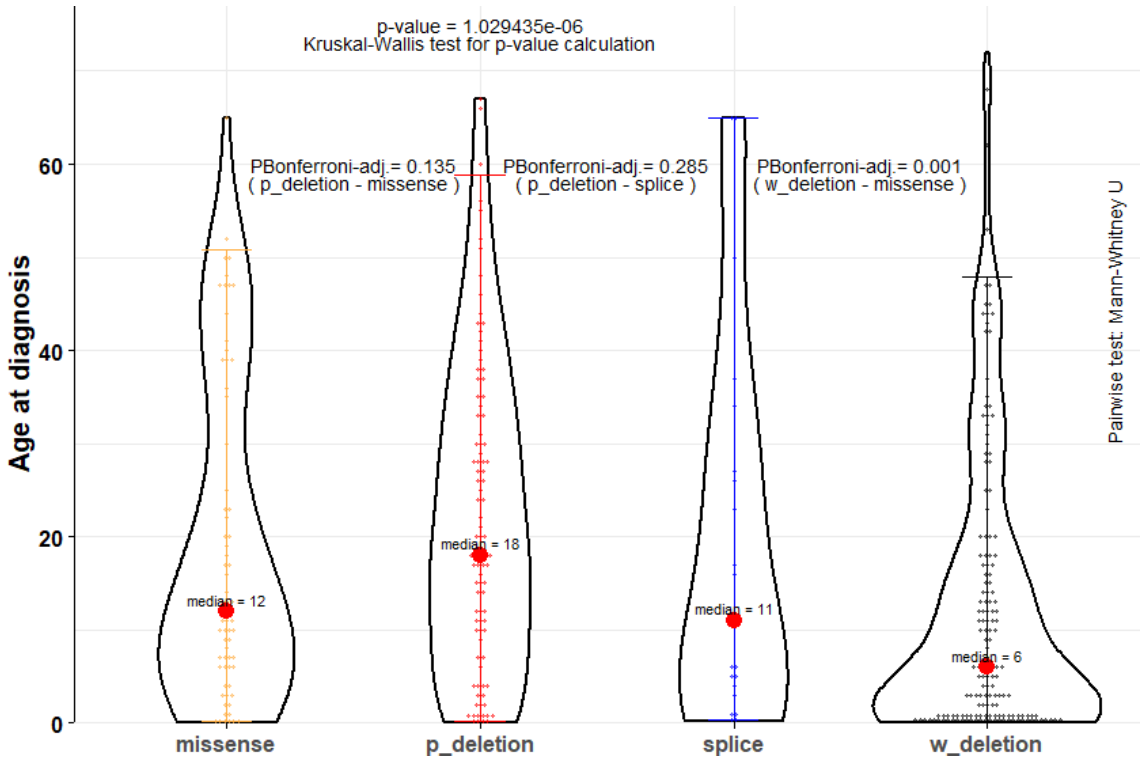

Figure 5. Violin Plots Illustrating Age at Diagnosis of HNF1B Nephropathy Across Various HNF1B Mutation Types.

Kidney Function Analysis

Among the cohort of 237 patients diagnosed with HNF1B nephropathy, eGFR data at the time of diagnosis was available for analysis. For 67 individuals within this subset, eGFR was computed using the MDRD formula. For the remaining patients, eGFR values were provided, determined through either MDRD or CKD-EPI calculation methods. Figure 6 illustrates the results of correlation analysis, indicating a statistically significant relationship between eGFR and age at diagnosis ($P < 0.001$). The analysis reveals a weak negative linear correlation (Spearman's rank correlation coefficient = - 0.26), suggesting that older age at diagnosis is associated with lower eGFR levels.

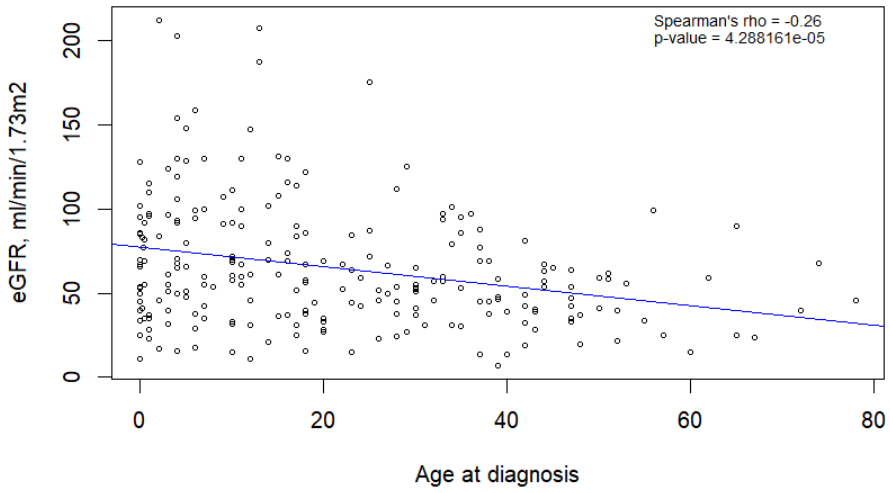

Figure 6. Age-eGFR Scatter Plot at HNF1B Nephropathy Diagnosis.

A linear regression analysis was conducted, revealing that for each one-year increase in age at diagnosis, the eGFR decreased by approximately 1.169 ml/min/1.73m², and this decrease was statistically significant (P = 0.02). However, it is important to note that the R-squared value of 0.35 indicates that approximately 35% of the variance in eGFR can be explained by age, suggesting that other variables may also play a significant role in determining eGFR levels.

Changes in kidney function, as inferred from variations in eGFR during the progression of HNF1B nephropathy, were assessed utilizing data from 57 patients. Among this cohort, eGFR calculations were performed using the MDRD formula for 20 patients. For the remaining patients, whose eGFR had already been determined, the CKD-EPI formula was employed. The relationship between eGFR and the duration of follow-up was found not to be statistically significant (P = 0.07), with a weak negative linear correlation observed (Spearman's rank correlation coefficient = - 0.24), though weaker than the correlation between age and eGFR at diagnosis (Figure 7).

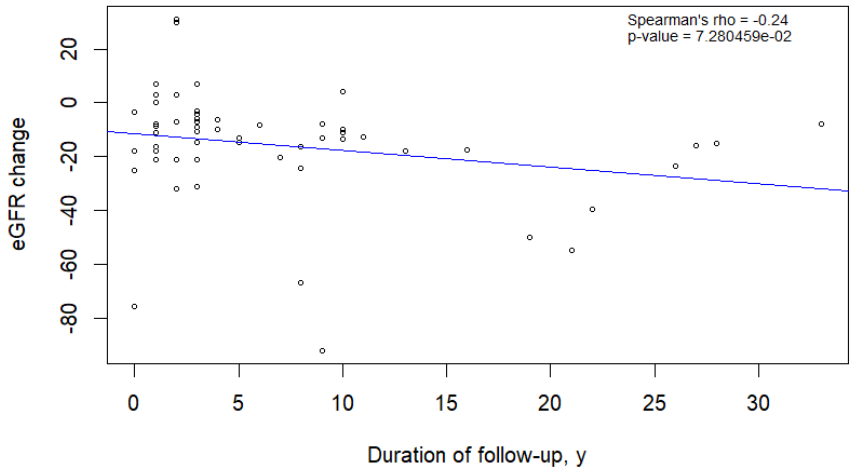

Figure 7. eGFR Change Over Time from HNF1B Nephropathy Diagnosis to Last Follow-up.

A spaghetti plot was utilized to examine eGFR changes during the follow-up period (Figure 8), revealing a weak negative linear trend of declining eGFR during HNF1B nephropathy follow-up period. The relationship between eGFR change during the follow-up period and follow-up duration was statistically significant (P = 0.01), with an average yearly eGFR decline during follow-up across all individuals of -2.56 ml/min/1.73m^2 per year.

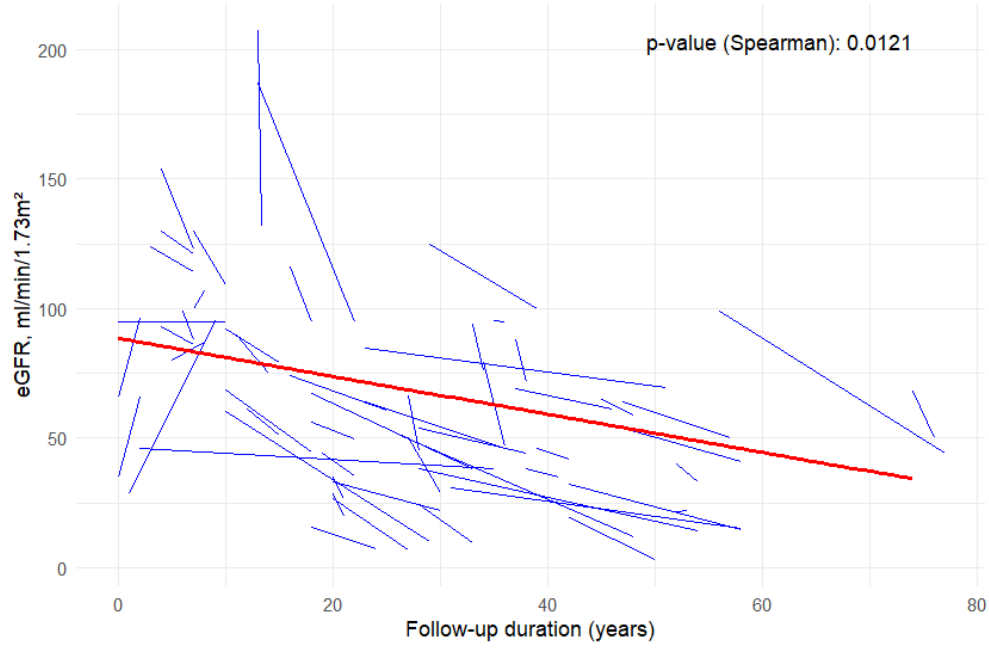

Figure 8. eGFR Change Trajectory During HNF1B Nephropathy Follow-up Period.

Estimated GFR at the time of last follow-up was reported for 121 patients. Among this cohort, eGFR calculations were performed using the MDRD formula for 23 patients. For the remaining patients, whose eGFR had already been determined, the CKD-EPI formula was employed. A statistically significant relationship was found between eGFR and age at HNF1B nephropathy last follow-up ($P < 0.001$), with a strong negative linear correlation (Spearman's rank correlation coefficient = - 0.53), suggesting that worse kidney function was observed in older patients (Figure 9).

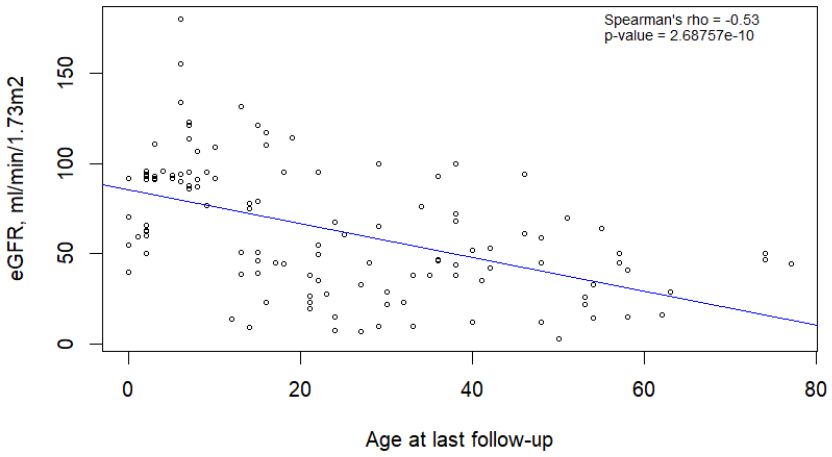

Figure 9. Age-eGFR Scatter Plot at HNF1B Nephropathy Last Follow-up.

After employing a linear regression model to assess the impact of age at HNF1B nephropathy diagnosis, eGFR at diagnosis, and follow-up duration on eGFR change during follow-up, with a cohort of 61 patients, it was revealed that these three predictors collectively explain approximately 52% of eGFR change variations (adjusted R-squared: 0.52) (Table No. 2). Notably, older age at diagnosis and higher eGFR at diagnosis emerged as more statistically significant predictors for eGFR change than follow-up duration, with highly significant results ($P < 0.001$).

Table No. 2. Linear Regression Model for eGFR Change During HNF1B Nephropathy Follow-up.

Explanatory variable	Estimate	P-value
Age at diagnosis	-0.73	<0.001
eGFR at diagnosis	-0.50	<0.001
Follow-up duration	-1.27	0.001

Figure 10 illustrates the distribution of CKD stages among 273 patients at the time of HNF1B nephropathy diagnosis. Patients were categorized into three age groups: 0-20 years (n = 171), 20-40 years (n = 59), and >40 years (n = 43). Notably, across all age categories, the majority of patients presented with CKD stages 2-3 (n = 78, 45%; n = 37, 63%; n = 28, 65%, respectively). Conversely, as the age groups advanced, there was a decline in the prevalence of CKD stage 1 patients (n = 74, 43%; n = 10, 17%; n = 3, 7%), coupled with a corresponding rise in the frequency of CKD stage 4-5 patients (n = 19, 11%; n = 12, 20%; n = 12, 28%). Statistical analysis revealed a highly significant association between age intervals and CKD stages (P < 0.001). Additionally, among the 22 patients who progressed to end-stage kidney disease (ESKD) (eGFR <15) at the time of HNF1B nephropathy diagnosis, the median age was 29 years (IQR: 36,5 years), ranging from 0.1 to 66 years.

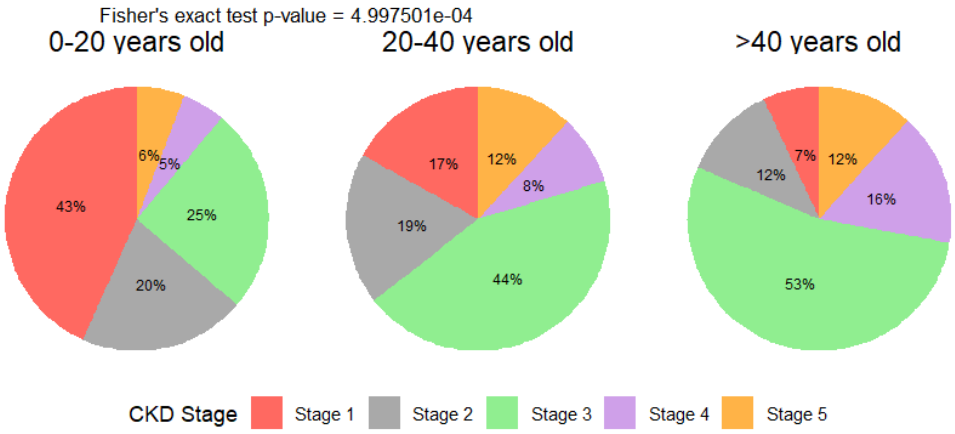

Figure 10. Distribution of CKD Stages at HNF1B Nephropathy Diagnosis Among Different Age Groups.

In Figure 11, pie charts illustrate the distribution of CKD stages at the last follow-up among 127 patients classified into three age groups: 0-20 years (n = 62), 20-40 years (n = 39), and >40 years (n = 26). Of these patients, 66 had a single CKD stage recorded solely at the last follow-up, while 61 had data for both the diagnosis and follow-up CKD stages. Among the latter group, the median follow-up duration was 3 years (IQR: 7.7 years), spanning from 0.2 to 33 years. The majority of patients in the 20-40 and >40 years age categories predominantly exhibited CKD stages 2-3 (n = 20, 51%; n = 15, 58%). Conversely, within the 0-20 years age category, the majority presented with CKD stage 1 (n = 33, 53%). Furthermore, in the age groups of 20-40 and >40 years, a similar proportion of patients displayed CKD

stages 4-5 (n = 15, 39%; n = 10, 38%, respectively). A statistically significant association between age intervals and CKD stages was observed (P < 0.001). Additionally, among the 16 patients who progressed to ESKD (eGFR <15) at the last follow-up, the median age was 32 years (IQR: 25.5 years), ranging from 10 to 58 years.

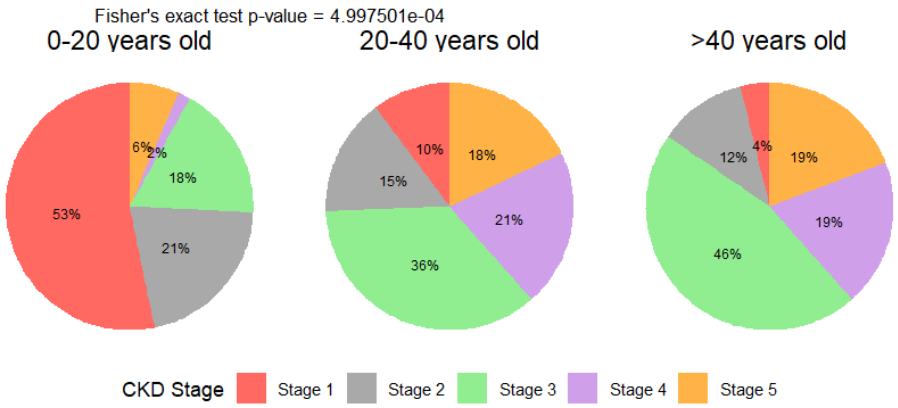

Figure 11. Distribution of CKD Stages at HNF1B Nephropathy Last Follow-up Among Different Age Groups.

Figure 12 illustrates the distribution of CKD stages according to the HNF1B mutation type at the last follow-up for a cohort of 115 patients. The differences between groups showed borderline statistical significance (P = 0.048), with highest CKD stages in patients with partial deletions (CKD stages 4-5, n = 13, 31.7%) and lowest in patients with whole gene deletions (CKD stage 1, n = 19, 47.5%). CKD stages 3-5 were less frequent in patients with HNF1B partial and whole gene deletions (n = 24, 58%; n = 13, 32.5%, respectively) than in patients with HNF1B mutations (missense: n = 19, 65.5%; splice site: n = 3, 60%, respectively).

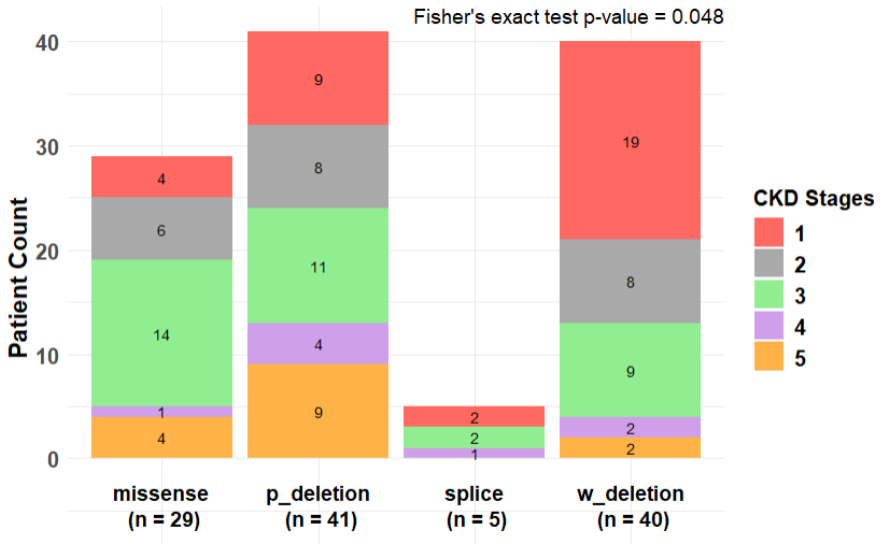

Figure 12. CKD Stages by HNF1B Mutation Types at Last Follow-up.

To explore long-term kidney outcomes during HNF1B nephropathy, the probability of not developing CKD stages 3, 4, and 5 during the follow-up period in 127 patients was analyzed using Kaplan-Meier survival curve (Figure 13). The analysis showed that at the age of 22 years, 25% of patients already had CKD stages 3 or higher that increased to 50% at the age of 38 years and 75% at the age of 53.

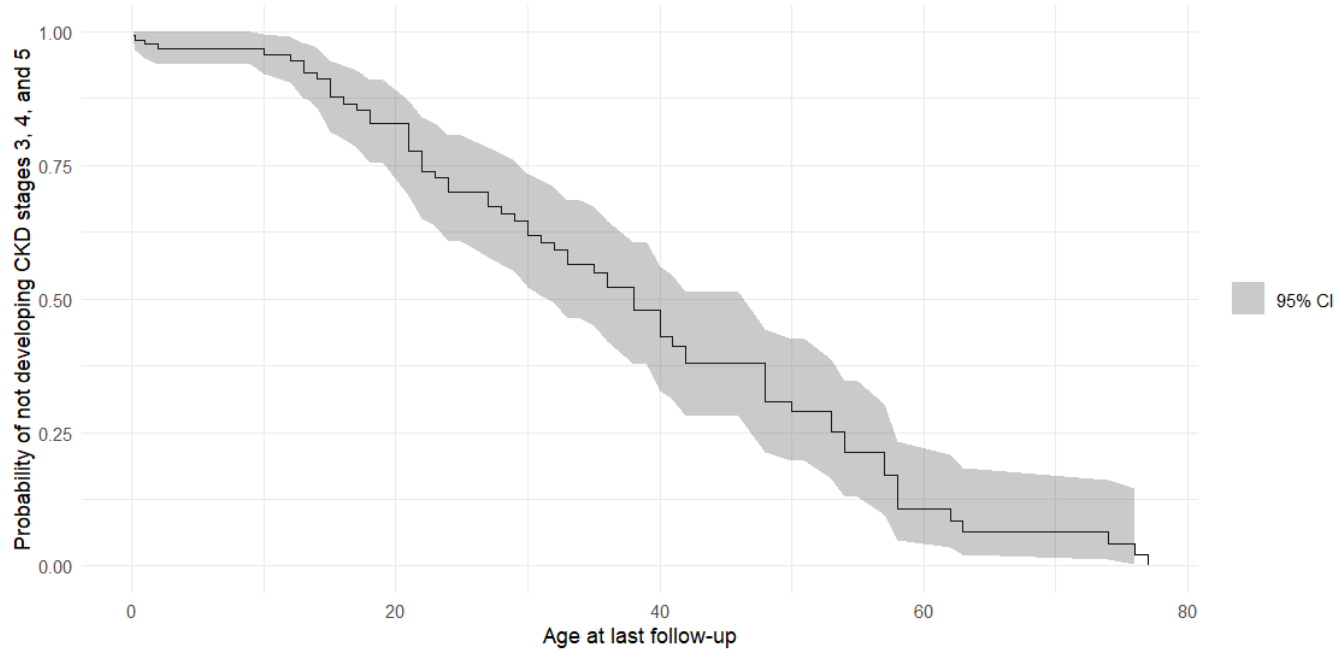

Figure 13. Probability of Avoiding Advanced CKD Stages During HNF1B Nephropathy Follow-up.

To further explore long-term kidney outcomes during HNF1B nephropathy, the probability of not developing CKD stage 5 during the follow-up period in 127 patients was analyzed using Kaplan-Meier survival curve (Figure 14). The analysis showed that at the age of 29 years, 10% of patients already had CKD stage 5 that increased to 25% at the age of 47 years and 40% at 58. In conclusion, there is a clear inverse relationship between age and the probability of not developing ESKD, indicating that patients diagnosed with HNF1B nephropathy over an extended period are at an increased risk of progressing to ESKD.

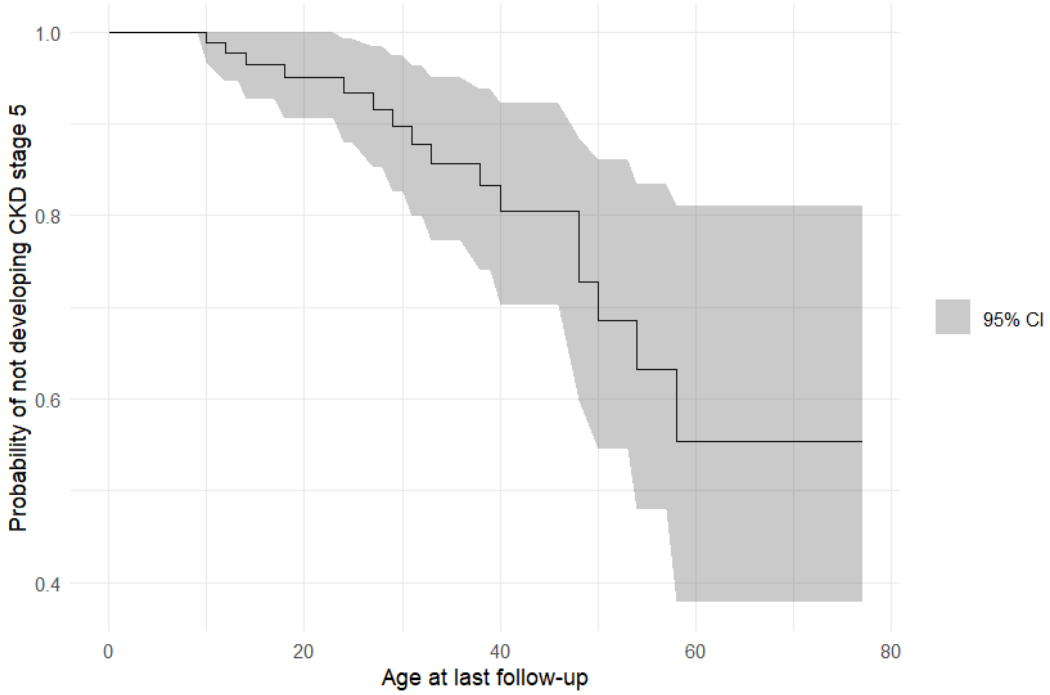

Figure 14. Probability of Avoiding CKD Stage 5 During HNF1B Nephropathy Follow-up.

Kidney Morphology and Kidney – Associated Complications Analysis

Prenatal kidney US data were available for 130 subjects. Hyperechogenic kidneys were the most prevalent finding, observed in 62.3% of cases, followed by kidney cysts (19.23%), cystic and multicystic kidneys (10%), and multicystic dysplastic kidneys (7.7%). Less common findings included hypoplastic kidneys and dysplastic kidneys.

Moving forward to the time of HNF1B nephropathy diagnosis, kidney US imaging data were reported for 438 patients. Kidney cysts emerged as the most prevalent finding, affecting 68% of patients, followed

by hyperechogenic kidneys (27.6%), dysplastic kidneys (18.5%), and multicystic dysplastic kidneys (11.2%). Less frequent observations included hydronephrosis and nephrocalcinosis.

At the last follow-up, kidney US imaging data were available for 63 patients, with kidney cysts remaining the predominant finding (73%). This was consistent with observations at the time of HNF1B nephropathy diagnosis. Additional findings included hypoplastic kidneys (15.9%), hyperechogenic kidneys (12.7%), and less frequently observed conditions such as nephrocalcinosis and multicystic dysplastic kidneys.

The prevalence of two kidney-associated complications, hypertension, and proteinuria, was assessed in patients with HNF1B nephropathy during their last evaluation (Figure 15). Data regarding hypertension status were available for 119 patients, while information on proteinuria was accessible for 150 patients. The graph illustrates that the majority of HNF1B nephropathy patients did not exhibit hypertension (n = 100, 84%) or proteinuria (n = 91, 61%) at last evaluation. Notably, the prevalence of proteinuria (n = 59, 39%) exceeded that of hypertension (n = 19, 16%).

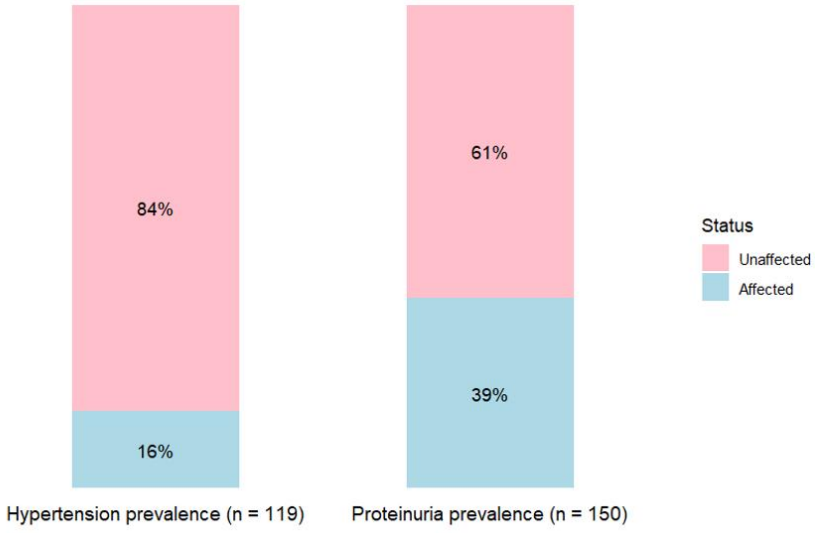

Figure 15. Prevalence of Kidney - Associated Complications at Last Evaluation in HNF1B Nephropathy Patients.

The assessment of hypertension status prevalence across mutation types included 90 patients with available data at last evaluation (Figure 16). Although variations were noted, no statistically significant relationship was found (P = 0.49). Hypertension was most frequently observed in the whole HNF1B gene deletion group (n = 6, 27%), while absent in the HNF1B missense mutation group.

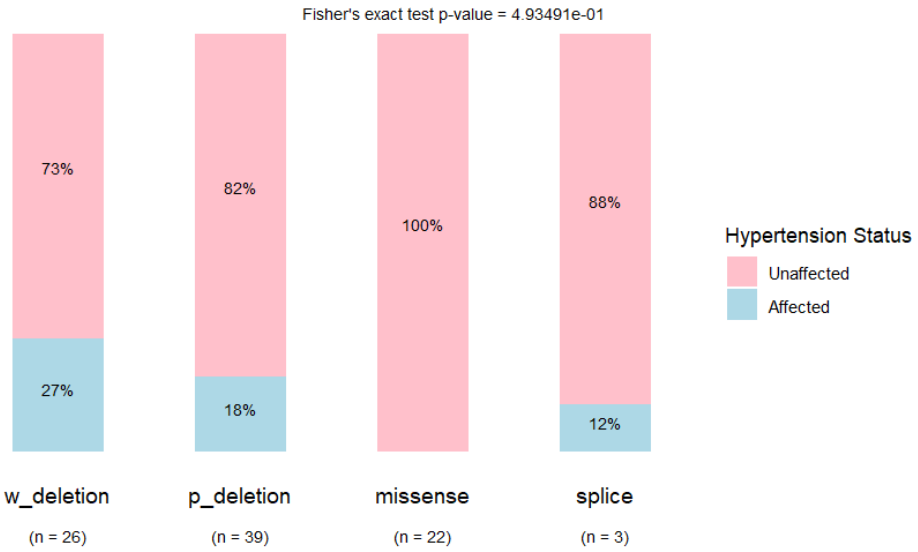

Figure 16. Hypertension Prevalence by HNF1B Mutation Types at Last Evaluation in HNF1B Nephropathy Patients.

The analysis of proteinuria status prevalence according to mutation type involved 99 patients with available data at last evaluation (Figure 17). Significant differences were observed (P = 0.008) with the lowest proteinuria frequency in the whole gene deletion group (n = 4, 19%). Patients with splice site mutations were excluded from analysis due to the very small number of patients with proteinuria status data available.

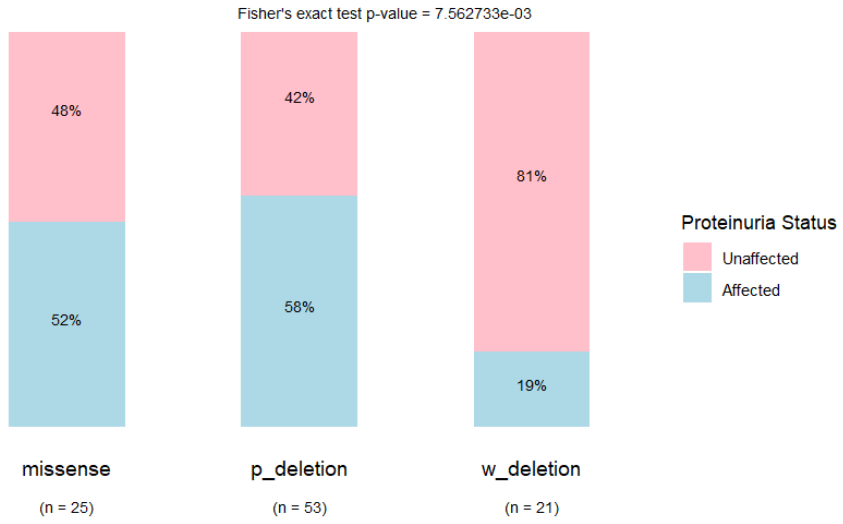

Figure 17. Proteinuria Prevalence by HNF1B Mutation Types at Last Evaluation in HNF1B Nephropathy Patients.

Extrarenal Manifestations Analysis

Data regarding diabetes status at last evaluation were available for 422 patients, while information on hypomagnesemia and hyperuricemia status was accessible for 318 and 322 patients, respectively. Analysis of the data revealed that the majority of HNF1B nephropathy patients did not exhibit diabetes (n = 259, 61%), hypomagnesemia (n = 217, 68%), or hyperuricemia (n = 189, 59%) at their last evaluation (Figure 18). Hyperuricemia emerged as the most prevalent extrarenal manifestation (n = 133, 41%), followed by diabetes (n = 163, 39%) and hypomagnesemia (n = 101, 32%).

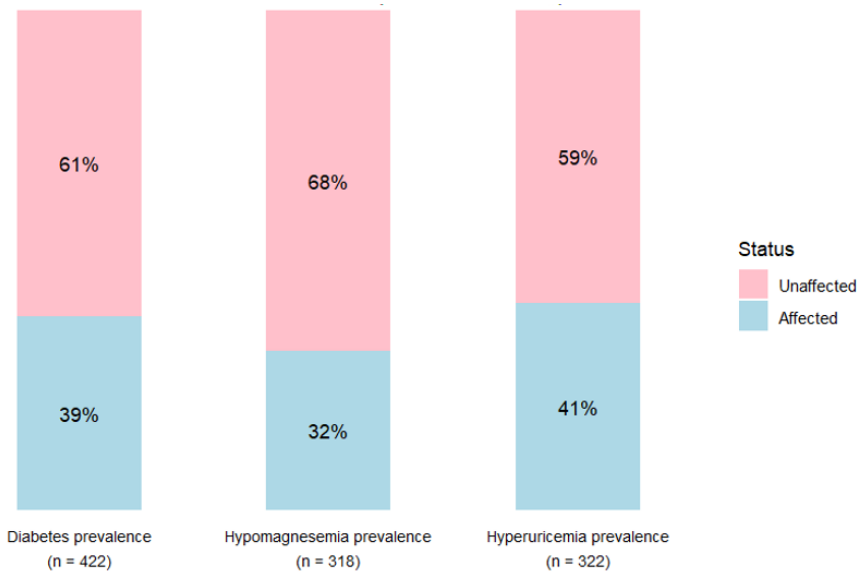

Figure 18. Prevalence of Extrarenal Manifestations at Last Evaluation in HNF1B Nephropathy Patients.

Figure 19 presents an analysis of diabetes prevalence across different HNF1B mutation types. The study encompassed data from 336 patients with known diabetes status at their last evaluation, along with information regarding HNF1B mutation types. The analysis did not reveal significant differences in the prevalence of diabetes according to mutation type (P = 0.088).

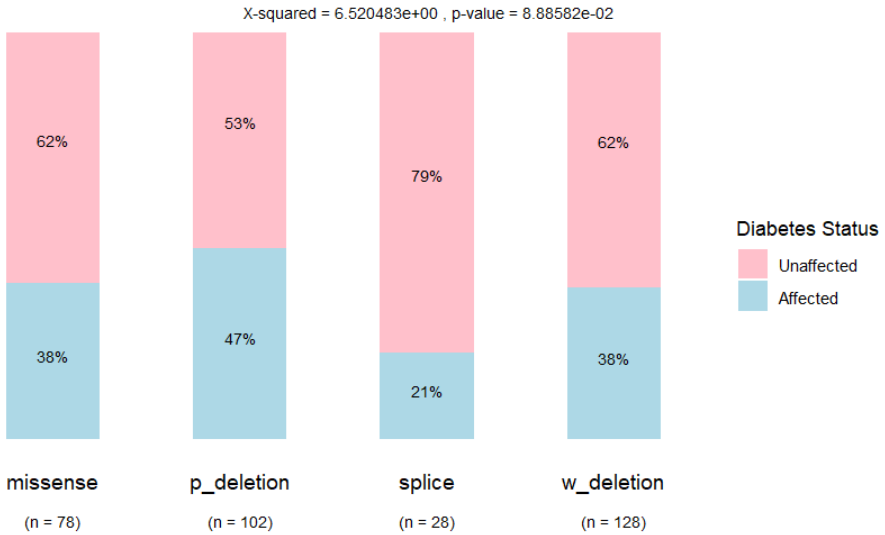

Figure 19. Diabetes Prevalence by HNF1B Mutation Types at Last Evaluation in HNF1B Nephropathy Patients.

The analysis of hyperuricemia prevalence according to mutation type involved 252 patients with available data at last evaluation (Figure 20). Significant differences (P = 0.002) were observed with the highest hyperuricemia frequency in the splice site mutation group (n = 14, 52%).

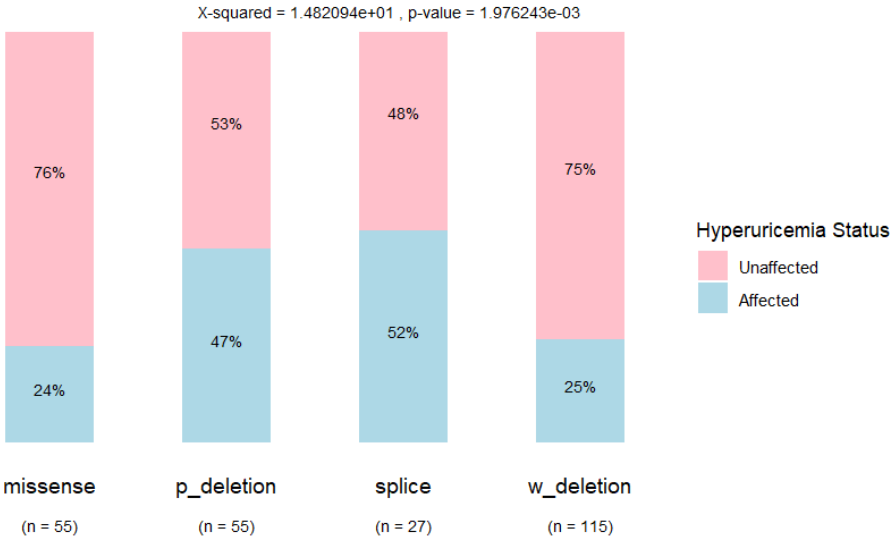

Figure 20. Hyperuricemia Prevalence by HNF1B Mutation Types at Last Evaluation in HNF1B Nephropathy Patients.

The analysis of hypomagnesemia prevalence according to mutation type involved 220 patients with available data at last evaluation (Figure 21). Significant differences (P = 0.006) were observed with the highest hypomagnesemia prevalence in the partial HNF1B gene deletion group (n = 22, 42%).

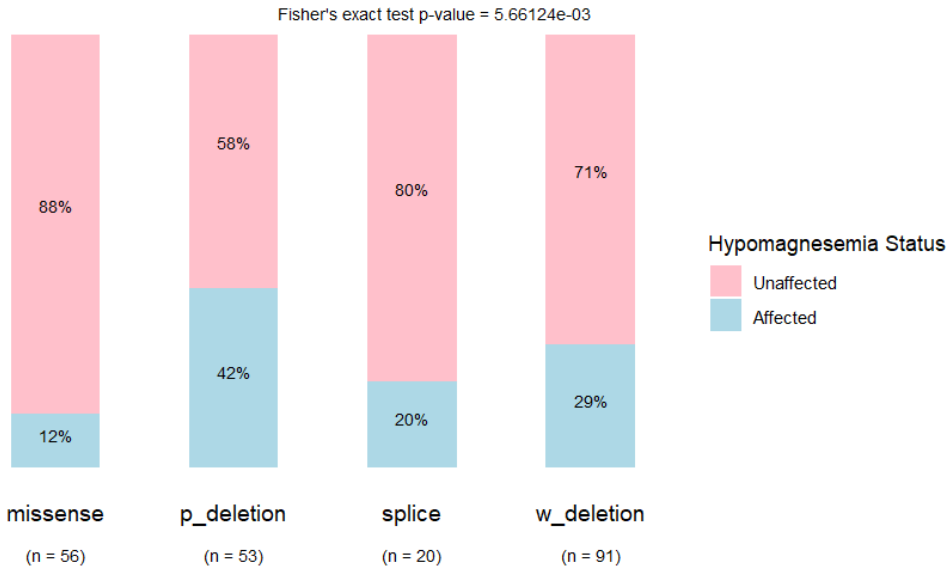

Figure 21. Hypomagnesemia Prevalence by HNF1B Mutation Types at Last Evaluation in HNF1B Nephropathy Patients.

Figure 22 depicts the cumulative incidence of diabetes cases among 111 patients with known age at diabetes onset. The median age of diabetes onset was 22 years (IQR: 19.5 years), ranging from 1 to 65 years old, with 74 patients being adults. The graph illustrates that 50% of diabetes cases occurred by age 22, with 75% diagnosed by age 34, suggesting a trend towards later diagnosis ages. Notably, less than 10% of cases were diagnosed before the age of 10. Analysis further categorized the diabetes onset ages: 6.3% of diabetes diagnoses (n = 7) occurred between ages 0 and 10, 32.4% (n = 36) between 10 and 20, 46.8% (n = 52) between 20 and 40, 13.5% (n = 15) between 40 and 60, and 0.9% (n = 1) over 60 years old.

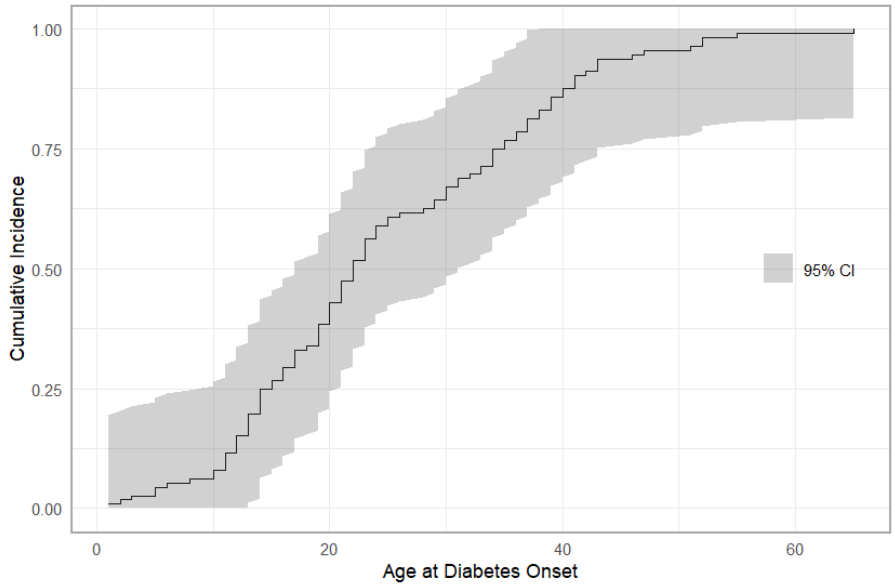

Figure 22. Cumulative Incidence of Diabetes in HNF1B Nephropathy Patients.

The assessment of diabetes prevalence across various age groups at the time of HNF1B nephropathy diagnosis encompassed 305 patients (Figure 23). Significant variations ($P < 0.001$) were noted, with the highest diabetes occurrence frequency observed in the >60 years age group (n = 9, 82%), followed by the 20-40 years age group (n = 54, 67%).

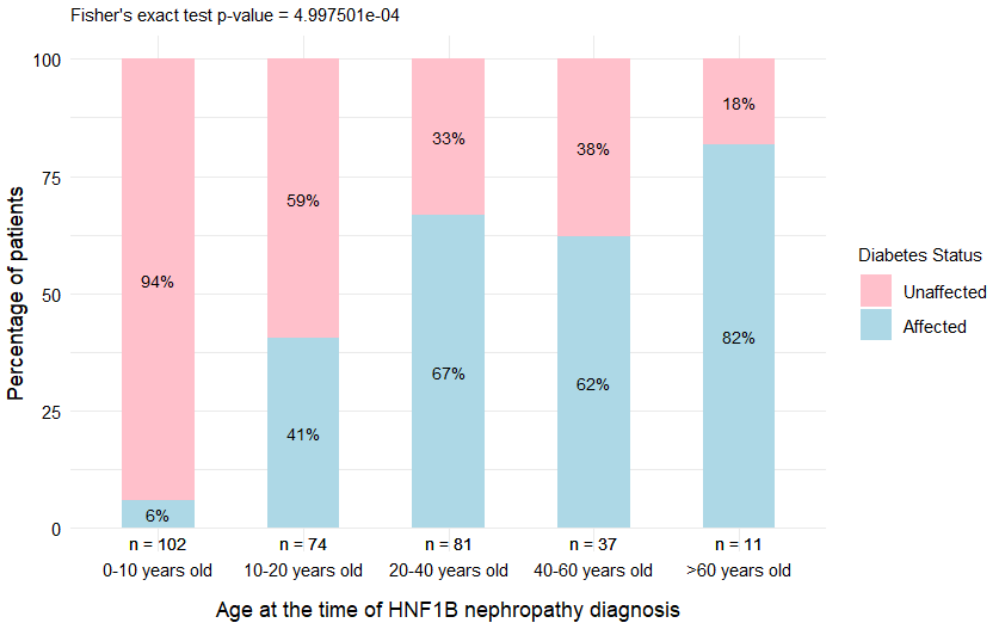

Figure 23. Prevalence of Diabetes at the Time of HNF1B Nephropathy Diagnosis.

DISCUSSION

Genetics

The prevalence and spectrum of HNF1B mutations in HNF1B nephropathy patients have been extensively documented in scientific literature. Notably, a significant proportion of these mutations consist of heterozygous whole-gene deletions, ranging from 43% to 64%, often associated with 17q12 chromosomal microdeletion (3,4,6,23,33,101,102). Conversely, the remaining cases predominantly present with heterozygous intragenic point mutations (3,4,6). The data presented in this analysis supports these findings, revealing whole HNF1B gene mutations as the most prevalent mutation type across all age groups up to 50 years old. Specifically, in this study, 45% of patients presented with whole HNF1B gene deletions, 26% exhibited partial HNF1B gene deletions, 21% had HNF1B missense mutations, and 7.5% presented with HNF1B splice site mutations. Consistent with these observations, a study by Okorn et al. demonstrated a similar distribution pattern of HNF1B mutation types, with 53% of patients exhibiting whole HNF1B gene deletions, 18% having HNF1B missense mutations, and 18% presenting with HNF1B splice site mutations or gross insertions (23).

Additionally, the occurrence of de novo mutations in both heterozygous intragenic and heterozygous whole-gene HNF1B mutations has been well-documented, accounting for up to 50% of cases (4,6,23) or 50% of cases in other studies (3). In this analysis, de novo mutations comprised 52% of cases, aligning closely with existing literature.

Kidney Function

Progressive kidney function decline throughout adulthood is considered a hallmark of HNF1B disease (3). However, in this review, at 22 years of age, 25% of analyzed patients already exhibited CKD stages 3 or higher, a proportion that increased to 50% at 38 years and 75% at 53 years. Furthermore, the incidence of CKD stage 5 patients also gradually increased over time, with 10% of patients reaching CKD stage 5 at 29 years, 25% at 47 years, and 40% at 58 years. Rapid and unexplained deterioration of kidney function has also been documented in scientific literature (6, 101), with Okorn et al. reporting a subset of HNF1B patients developing ESKD before the age of 2 years (23).

Scientific articles report a median yearly eGFR decrease of −2.45 ml/min/year (3,6,101), comparable to the observed average yearly eGFR decline during follow-up in this review (-2.56 ml/min/1.73m² per year, P = 0.01). Interestingly, the observed average yearly eGFR decline differs from that calculated using linear regression analysis (1.169 ml/min/1.73m², P = 0.02), resembling the mean annual eGFR loss

reported by Okorn et al. in their total study cohort (− 1.0 ml/min/1.73m²) (23). Dubois-Laforgue et al. concluded that eGFR at follow-up strongly correlates with eGFR at diagnosis and with age at follow-up (101), aligning with this study's observation of a strong negative correlation (Spearman's rho = -0.53, $P < 0.001$) between eGFR and age at last follow-up. Additionally, linear regression analysis indicated that lower eGFR and older age at diagnosis were more statistically significant predictors for changes in eGFR compared to the duration of follow-up ($P < 0.001$).

Regarding the prevalence of different CKD stages at HNF1B nephropathy diagnosis, kidney function tends to be well-preserved, with the majority of patients having CKD stage 1 or stage 2 (91.2%, Kołbuc et al; 88%, Okorn et al) (102,23). In contrast, this review indicated a worse kidney function profile, with the majority of patients across all age categories presenting with CKD stages 2-3 (0-20 years: 45%, 20-40 years: 63%, >40 years: 65%, respectively). CKD stage 1 was predominant only in the 0-20 years age group (43%). Moreover, while Okorn et al. reported no CKD stage 5 patients (23), the cohort from this study revealed 6% in the 0-20 years age group and 12% in the 20-40 and >40 age groups. It's worth noting that the study cohorts in Kołbuc et al. and Okorn et al. had a mean age of 7.84 years (95% CI: 6.10-9.58) (102) and were all <18 years old (23), respectively, unlike this study where the majority of patients were adults, potentially influencing the prevalence of worse CKD stages at diagnosis in this review.

In their study, Faguer et al. followed 27 patients for a median duration of 5.5 years (range: 1–29), with a median age of 35 years (range: 16–74) at the latest follow-up (3). Conversely, this review had a median follow-up duration of 3 years (IQR: 7.7 years), reflecting a similar age distribution at last follow-up to the Faguer et al. study.

Both Faguer et al. and Dubois-Laforgue et al. reported a notable prevalence of CKD stages 3-4 at the latest follow-up, with rates of 60% and 44%, respectively (3,101). In this study, a significant proportion of patients aged 20-40 years and >40 years primarily exhibited CKD stages 2-3 (51% and 58%, respectively). Moreover, the frequency of CKD stages 4-5 at the last follow-up was comparable between this study (20-40 years: 39%, >40 years: 38%) and the findings reported by Faguer et al. (39%) (3).

Of particular interest is the age category of 0-20 years, where the majority of patients in this review presented with CKD stage 1 at last follow-up (53%), contrasting with the findings of Faguer et al. (8%) (3), but aligning with Okorn et al., where 58% of patients exhibited CKD stage 1 at the last follow-up (23). The median age of patients in the Okorn et al. study was 8 years (range 0–19 years) (23), corresponding to the 0-20 years age group in this review. Additionally, within the 0-20 years age group,

21% of patients in this study had CKD stage 2 (compared to 24% in the Okorn et al. study), and 6% progressed to ESKD (compared to 8% in Okorn et al. for patients <2 years old, and 3% in patients >2 years old, with a median age of 12 years, range 5–19 years) (23).

Regarding ESKD at last follow-up, Faguer et al. reported a considerable proportion of patients progressing to this stage, with rates of 15% (3). Notably, they observed instances of ESKD onset at diverse ages, with four patients reaching ESKD at ages 7, 22, 29, and 31 years (3). In this study, 12% of patients reached ESKD, with a median age of 32 years (IQR: 25.5 years), ranging from 10 to 58 years.

Regarding genotype-kidney function correlations, Okorn et al. concluded no statistically significant differences in kidney function or phenotypes among carriers of different HNF1B mutation types (23). However, this review indicated borderline statistical significance in CKD stage differences among different mutation types (P = 0.048). Dubois-Laforgue et al. reported less frequent CKD stages 3-5 in patients with HNF1B deletions than in those with mutations (101), a trend also observed in this review: CKD stages 3-5 were less frequent in patients with HNF1B partial and whole gene deletions (58%, 32.5%) than in patients with HNF1B mutations (missense 65.5%, splice site 60%). Additionally, this review identified the highest CKD stages in patients with partial deletions (CKD stages 4-5, 31.7%) and the lowest in patients with whole gene deletions (CKD stage 1, 47.5%).

Kidney Morphology

Kidney structural abnormalities represent a significantly heterogeneous characteristic of HNF1B nephropathy (6). Heidet et al. identified isolated hyperechogenic kidneys as the most prevalent prenatal US feature in HNF1B nephropathy patients, accounting for 61% of cases (33), a finding consistent with this review where 62% exhibited this feature. Other prenatal kidney US features, such as multicystic dysplastic kidneys, were less common, with rates of 18% in the Heidet et al. study (33) and 7.7% in this review. Kołbuc et al. also observed a higher prevalence of hyperechogenic and multicystic dysplastic kidneys in patients with HNF1B mutations (102).

A cystic phenotype is frequently noted in HNF1B nephropathy patients across various studies (3, 6, 102). Dubois-Laforgue et al. reported kidney cysts in 81% of their patient cohort (101), rather consistent with this finding that kidney cysts affected 68% of patients at the time of HNF1B nephropathy diagnosis. Okorn et al. found bilateral and unilateral kidney cysts in kidney US at the end of follow-up in 90% of

their patients (23), while Faguer et al. detected kidney cysts in 62% of patients at their last follow-up (3). In this review, kidney cysts were also the predominant finding (73%) at the last follow-up kidney US. Additionally, a range of kidney manifestations, including hydronephrosis, vesicoureteral reflux, and nephrocalcinosis, have been reported in cases of HNF1B nephropathy (6). In this review, hydronephrosis was observed in 3% of kidney ultrasound findings (n = 14), while vesicoureteral reflux and nephrocalcinosis were identified in 2% (n = 8) and 1% (n = 4) of cases, respectively.

Prevalence of Kidney – Associated Complications and Extrarenal Manifestations

The kidney - associated complications phenotype of HNF1B nephropathy is predominantly characterized by a low prevalence of arterial hypertension (6). Faguer et al. corroborated these findings, reporting a hypertension frequency of only 7% among their study participants (3). In contrast, this review observed a hypertension prevalence of 16%.

Regarding proteinuria, Dubois-Laforgue et al. reported a prevalence of 26%, whereas this review found a higher frequency of 39% among HNF1B nephropathy patients (101).

The prevalence of hyperuricemia in this review was 41%, mirroring that of other studies, such as Kołbuc et al. (42.5%) and Okorn et al. (37%) (102,23). Similarly, the frequency of hypomagnesemia in this review was 32%, which fell within the range reported by other studies but was lower than some previous findings (Dubois-Laforgue et al.: 75%, Kołbuc et al.: 65%, Faguer et al.: 62%) or higher (Okorn et al.: 24%) (101,102,3,23).

In terms of diabetes prevalence, this review found it to be 39%, which was higher than that reported by Faguer et al. (9%) (3) but lower than the frequency in Dubois-Laforgue et al. study (82%) (101). Notably, the median age at onset of diabetes in this review was 22 years, with 61% of patients experiencing onset after the age of 20. These findings are similar to the ones from Dubois-Laforgue et al. study, where over 25 years was the age of onset for diabetes in 57% of patients (101). Faguer et al. reported a median age of 37 years for HNF1B nephropathy patients with diabetes at last follow-up (3). However, it is likely that differences in the age distribution of patients across these study cohorts influenced the disparate diabetes prevalence numbers. Diabetes mellitus is commonly observed in approximately 50% of HNF1B nephropathy patients and represents the most frequent extrarenal feature associated with the disease (6). Additionally, the presence of CKD at the onset of diabetes is a common occurrence, with 40% of patients in this review already having diabetes at the time of HNF1B nephropathy diagnosis.

Genotype – Phenotype Correlations

Scientific literature suggests that no clear correlation between the type or position of a pathogenic variant within the HNF1B gene and the occurrence of specific clinical features has been established to date (4,6). However, this analysis revealed distinct associations between mutation types and clinical manifestations. Notably, the lowest prevalence of proteinuria was observed in the whole gene deletion group (19%), while the highest was in the partial gene deletion group (58%) (P = 0.008). However, only 19% of the entire patient cohort (n = 99) had available data regarding proteinuria prevalence, similar to the number of patients with data on hyperuricemia frequency (48%, n = 252) and hypomagnesemia prevalence (42%, n = 220). The lowest frequency of hyperuricemia and hypomagnesemia was observed in the missense mutation group (24%, P = 0.002; 12%, P = 0.006, respectively). Conversely, the splice site mutation group exhibited the highest prevalence of hyperuricemia (52%). Kołbuc et al. also noted a higher frequency of hyperuricemia in patients with point mutations compared to deletions of the HNF1B gene (102). In this review the frequency of hyperuricemia among patients with HNF1B point mutations and deletions was similar (76% and 72%, respectively). Additionally, the partial HNF1B deletion group showed the highest frequency of hypomagnesemia in this study (42%). These observed associations underscore the intricate interplay between genotype and phenotype in HNF1B nephropathy, warranting further investigation.

Given the complex clinical landscape of HNF1B – associated disease, two types of scores have been proposed for selecting patients for genetic screening based on clinical criteria (6). The score proposed by Faguer et al. incorporates various factors such as family history, antenatal kidney abnormalities, kidney and urinary tract phenotypic changes, electrolyte or uric acid disorders, and pathological findings, among others. Notably, the presence of left or right kidney hyperechogenicity or kidney cysts, pancreas abnormalities, and genital tract abnormalities carries the highest weight (+4) in this scoring system (100).

CONCLUSIONS

The systematic literature review yielded the following main conclusions:

1. The prevalence and inheritance patterns of four HNF1B mutation types were analyzed. Whole HNF1B gene deletions were the most common mutation type across all age groups up to 50 years old. The median age of onset for HNF1B nephropathy varied among mutation types, with whole HNF1B gene deletions having the youngest median age at 6 years, followed by splice site

mutations at 11 years, and missense and partial HNF1B gene deletions at 12 and 18 years, respectively. Notably, de novo HNF1B mutations accounted for 52% of cases, while 48% were inherited.

2. Long-term kidney function outcomes and their associations with HNF1B mutation types were investigated. HNF1B nephropathy patients exhibited an increased risk of progression to end-stage kidney disease, with 10% reaching chronic kidney disease stage 5 by age 29 years at last follow-up, increasing to 25% at 47 years and 40% at 58 years. The average yearly decline in estimated glomerular filtration rate during follow-up was -2.56 ml/min/1.73m^2 per year, indicating progressive kidney function deterioration. Linear regression analysis identified older age and lower estimated glomerular filtration rate at diagnosis as statistically significant predictors for estimated glomerular filtration rate change ($P<0.001$). Notably, patients with whole HNF1B gene deletions exhibited the best – preserved kidney function, with 47.5% having stage 1 chronic kidney disease while those with partial gene deletions showed the poorest kidney function, with 31.7% presenting with chronic kidney disease stages 4 and 5 ($P = 0.048$).

3. Kidney ultrasound features of HNF1B nephropathy patients were analyzed, revealing hyperechogenic kidneys as the predominant prenatal phenotype (62%). Kidney cysts were most prevalent both at diagnosis (68%) and at last follow-up (73%).

4. The frequency and genotype – phenotype correlations of kidney - associated complications (such as hypertension and proteinuria) were examined. Proteinuria prevalence exceeded hypertension (39% and 16%, respectively), with the whole HNF1B gene deletion group presenting with the highest hypertension frequency (27%, $P = 0.49$) and the lowest proteinuria incidence (19%, $P = 0.008$). Proteinuria was most prevalent in the partial HNF1B gene deletion group (58%).

5. The prevalence and genotype – phenotype correlations of extrarenal manifestations (including diabetes, hyperuricemia, and hypomagnesemia) were assessed. Hyperuricemia was the most common extrarenal manifestation (41%), followed by diabetes (39%) and hypomagnesemia (32%). A trend towards later diabetes diagnoses was observed, with 50% of cases diagnosed by age 22, and the highest diabetes prevalence observed in the >60 years age group at the time of HNF1B nephropathy diagnosis (82%) ($P < 0.001$). The partial HNF1B gene deletion group exhibited the highest hypomagnesemia frequency (42%, $P = 0.006$) and diabetes incidence (47%,

P = 0.088), while hyperuricemia was most frequent in the HNF1B splice site mutation group (52%, P = 0.002).

In summary, the progressive decline of kidney function in HNF1B nephropathy patients underscores the importance of long-term monitoring for this population. Furthermore, findings from this review emphasize the need for further research to elucidate the underlying mechanisms driving genotype-phenotype correlations in HNF1B nephropathy.

PRACTICAL RECOMMENDATIONS

1. HNF1B-associated disease should be considered in patients presenting with hyperechogenic kidneys and kidney cysts, particularly in those with concurrent diabetes, hyperuricemia or hypomagnesemia, even without a positive family history.

2. Kidney function tends to decline gradually, thus regular monitoring is required. Consider older age at HNF1B nephropathy diagnosis and initial eGFR as predictors of more rapid kidney function decline.

3. Note that individuals with partial gene deletions demonstrate the highest incidence of hypomagnesemia and diabetes, while patients with whole gene deletions most commonly present with hypertension. Additionally, patients with splice site mutations exhibit the highest incidence of hyperuricemia.

4. Diabetes may manifest in adolescence, thus regular monitoring and advising families on symptom awareness is required.

In addition to these recommendations, further research may shed light on additional factors influencing the clinical course and management of HNF1B nephropathy. Specifically, investigating the impact of environmental factors, comorbidities, and therapeutic interventions on disease progression could provide valuable insights for optimizing patient care and outcomes in the future.

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SUPPLEMENTARY MATERIAL

Annex No. 1. Summary of Demographic, Genetic, and Clinical Data for Deceased Patients with HNF1B Nephropathy.

Ref.	No.	Sex	Age at death	HNF1B mutation	Cause of death
26	1	F	ND	ND	ESKD
33	2	ND	ND	complete HNF1B deletion	oligo-anamnios
33	3	ND	ND	partial HNF1B deletion. Exon 4. c.840delC, p.Pro280fs	enlarged multicystic kidneys
33	4	ND	ND	partial HNF1B deletion. Exon 1. c.232G→T. p.Glu78X	bilateral MCK
35	5	ND	22w	ND	polyhydramnios
35	6	ND	32w	heterozygous HNF1B deletion	unilateral enlarged multicystic kidney, polyhydramnios
40	7	M	37y	HNF1B splice site mutation. Intron 2. IVS2+1G>T	ESKD
50	8	F	27y	HNF1B in-frame deletion. R137-K161del	a condition resembling multiple sclerosis with progression of skeletal muscle paralysis
57	9	M	39y	HNF1B exons 1-9 deletion, yielding the mutation p.Met1_Trp557del	poorly treated MODY5

F: female. M: male. ND: not determined. ESKD: end-stage kidney disease. MCK: multicystic kidneys. MODY5: mature-onset diabetes of the young type 5.