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ORIGINAL ARTICLE

Prevalence and Characteristics of Specimens with Extremely Low High-Density Lipoprotein Cholesterol

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SUMMARY

Background: **Extremely low levels of high-density lipoprotein cholesterol (HDL-C), defined as < 10 mg/dL, are rarely observed in clinical laboratories and may result from severe metabolic disorders, genetic conditions, or analytical and preanalytical interferences. Understanding the prevalence and associated findings of such results is critical for accurate interpretation.**
Methods: **We retrospectively analyzed 1,022,234 HDL-C test results from specimens submitted to GC Labs, a large referral laboratory in South Korea, between January and December 2023. For specimens with HDL-C < 10 mg/dL, concurrent laboratory findings were evaluated. Additional comparisons of the prevalence of HDL-C < 10 mg/dL and its associated laboratory findings were made using public datasets from KNHANES (2011 - 2023), NHIS (2023), and US NHANES (2015 - 2020).**
Results: **Among all specimens, 147 (0.015%) showed HDL-C < 10 mg/dL. Out of these, 125 specimens had available concurrent test results. Common findings included abnormal liver chemistries (56.8%), decreased kidney function (31.2%), elevated CRP (20.0%), anemia, and very high triglyceride levels (≥ 500 mg/dL in 33.6%). Several patterns suggested preanalytical issues, including delayed serum separation, dilutional effects, or lipemic interference observed on gross examination (12.0%). One case showed no apparent abnormalities, raising suspicion of rare genetic or medical conditions or analytical error. Public datasets showed similarly low prevalence (0.004 - 0.009%) and comparable findings.**
Conclusions: **Extremely low HDL-C values are rare but often linked to identifiable biochemical abnormalities or preanalytical/analytical interferences. Reviewing concurrent test results and specimen handling helps distinguish true pathology from spurious results and improve diagnostic accuracy in clinical laboratories.**
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KEYWORDS

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INTRODUCTION

High-density lipoprotein cholesterol (HDL-C) plays an important role in reverse cholesterol transport [1-3]. Both low and high HDL-C levels have been reported to be associated with an increased risk of all-cause mortality [1,2,4,5]. In particular, extremely low HDL-C concentrations may indicate underlying metabolic disor-

ders, genetic conditions, or severe systemic illnesses [1-3,6]. Extremely low HDL-C, also referred to as severe HDL-C deficiency, is commonly defined as an HDL-C concentration of < 20 mg/dL and may result from various secondary causes, including severe hypertriglyceridemia, sepsis, burns, small bowel exclusion syndrome, use of androgenic steroids, liver disease, inflammation, lymphoproliferative disorders, paraproteinemia, antibodies to lecithin-cholesterol acyltransferase (LCAT), and certain medications [6-10]. These medications, including peroxisome proliferator-activated receptor agonists, fibrates, and recombinant interleukins, are often used to treat diabetes, dyslipidemia, and inflammatory diseases [6-10]. The mechanisms by which these diseases and drugs affect HDL-C levels are thought to involve either metabolic alterations in lipid metabolism or analytical interferences [1,6-11]. In addition to these secondary causes, primary genetic causes of extremely low HDL-C levels include variants in the ATP-binding cassette transporter A1 (*ABCA1*), *LCAT*, and apolipoprotein AI (*APOA1*) genes [1,2,12-14].

In clinical laboratories, knowledge of the prevalence and associated factors of extreme or suspicious test results is essential to minimize the risk of clinical errors and to enable proper interpretation, ultimately improving patient outcomes [15,16]. Although previous studies have investigated extremely low HDL-C levels in various populations, most used cutoffs of 20 mg/dL (0.52 mmol/L) or 15 mg/dL (0.39 mmol/L), corresponding to approximately the 0.1st percentile in the general population [1,4-6,11,13,17]. Despite its clinical significance, the prevalence and laboratory characteristics of specimens with markedly low HDL-C levels in routine clinical settings - across different institution sizes and patient populations - remain underexplored. Understanding the prevalence and common features of specimens with extreme HDL-C levels may help prevent misinterpretation of laboratory results and guide improvements in the management of preanalytical factors, such as analytical interference. These efforts are crucial for quality improvement in clinical laboratory practice [18].

Therefore, the aim of the present study was to investigate the prevalence of extremely low HDL-C levels, defined as < 10 mg/dL (0.26 mmol/L), as a rare and extreme event in clinical laboratory testing, and to characterize the associated biochemical profiles. Understanding these patterns may provide insights into potential diagnostic implications and help identify factors that contribute to spurious test results.

MATERIALS AND METHODS

Study subjects and design for this study

GC Labs, one of the largest referral clinical laboratories in South Korea, receives specimens for analysis from local clinics and hospitals without in-house laboratories across the country, with lipid tests - including HDL-C - being among the most commonly requested analytes in clinical practice [16]. We conducted a retrospective analysis of all HDL-C test results requested between January 1 and December 31, 2023, using the laboratory information system. All laboratory test results performed simultaneously on the same specimens were reviewed. Since hemolysis, icterus, and lipemia (HIL) indices were not routinely measured during this period, we reviewed the results of all concurrently ordered laboratory tests to identify possible preanalytical or analytical factors that may be associated with extremely low HDL-C levels.

The laboratory tests reviewed included lipid profiles (triglycerides and total cholesterol); liver chemistries (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP], total and direct bilirubin); serum total protein, albumin, amylase, lipase, uric acid, blood urea nitrogen (BUN), creatinine; electrolytes (sodium [Na], potassium [K], chloride [Cl]); inflammatory markers (C-reactive protein [CRP]); diabetes-related tests (serum glucose and glycated hemoglobin [HbA1c]); C-peptide, insulin, calcium, phosphorus, magnesium, creatine kinase (CK), lactate dehydrogenase (LDH); thyroid function tests (thyroid-stimulating hormone [TSH], free thyroxine [free T4], triiodothyronine [T3], free T3, and T4); vitamin B12; folate; complete blood counts (white blood cell [WBC] count, hemoglobin, hematocrit, and platelet count); and peripheral blood smear morphological evaluations, specifically for the presence of red blood cell agglutination suggestive of cold agglutinin (if available). For visibly turbid specimens, records of lipemic samples were also reviewed when available. The exclusion criteria were: 1) the absence of simultaneously measured triglyceride and total cholesterol levels, and 2) specimens with only limited laboratory data, in which no additional indirect information regarding specimen status was available (e.g. specimens tested only for lipid profiles or only for HbA1c). All lipid concentrations in this study were reported in mg/dL. The following conversion factors were applied: HDL cholesterol and total cholesterol were converted using mmol/L × 38.66 = mg/dL, and triglycerides were converted using mmol/L × 88.5 = mg/dL. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of GC Labs (GCL-2025-1017-01, April 14, 2025), which also granted a waiver of informed consent due to the retrospective nature of the study and the minimal risk posed to participants.

Definitions

We reviewed the distribution of all HDL-C test results to evaluate the specimen prevalence of extremely low HDL-C, defined as a concentration of < 10 mg/dL. Subsequently, we reviewed triglyceride and total cholesterol results to assess the association between extremely low HDL-C and other lipid parameters.

For lipid profile categorization, the National Cholesterol Education Program Adult Treatment Panel III (NCEP

ATP III) guidelines were applied: total cholesterol levels of 200 - 239 mg/dL were classified as borderline high, ≥ 240 mg/dL as hypercholesterolemia; triglyceride levels ≥ 200 mg/dL as hypertriglyceridemia, and ≥ 500 mg/dL as very high triglyceridemia [3]. To identify potential spurious results, we also evaluated the distribution of triglyceride and total cholesterol levels exceeding the upper limits of analytical measurement intervals (> 885 mg/dL for triglycerides and > 800 mg/dL for total cholesterol). Specimens with HDL-C < 10 mg/dL and triglycerides ≥ 500 mg/dL were considered suspicious for the presence of chylomicrons, endogenous unesterified glycerol, or other interferents [1,6]. Specimens with abnormalities in two or more liver chemistries were categorized as having abnormal liver chemistries [19,20]. Elevated C-reactive protein (CRP ≥ 0.5 mg/dL) was used as an indicator of possible inflammatory conditions [1,6,11,21]. Decreased kidney function was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73 m², calculated using the CKD-EPI 2009 equation based on serum creatinine [22,23]. Anemia was defined based on hemoglobin concentration as < 11.0 g/dL in women and < 12.0 g/dL in men [24]. As information on fasting status was unavailable, diabetes was assessed based on HbA1c ≥ 6.5% or serum glucose ≥ 200 mg/dL. Specimens were considered suspicious for dilutional effects or analytical interference when three or more concurrently tested analytes from the same serum sample showed abnormally low values [15,18]. In cases where serum potassium levels exceeded 6.0 mmol/L, delayed serum separation was suspected [18,22]. Specimens with total serum protein > 8.7 g/dL and a reversed albumin-to-globulin ratio were considered suspicious for paraproteinemia or other interfering substances [6,18].

Analytical methods in GC Labs

HDL-C, triglycerides, and total cholesterol were measured using enzymatic methods on the Cobas 8000 platform (Roche Diagnostics, Mannheim, Germany). HDL-C was measured with a homogeneous enzymatic colorimetric assay (HDL-C Gen.4), triglycerides were measured using TRIG reagent kits without glycerol blanking, and total cholesterol was measured using Cholesterol Gen.2 reagent kits, all provided by Roche Diagnostics and performed according to the manufacturer's instructions. All chemistry assays were performed on the Cobas 8000 platform using assay-specific reagents within a closed analytical system. The analytical methods used in this study at GC Labs were identical to those used in the 2022 and 2023 Korea National Health and Nutrition Examination Survey (KNHANES), as described on the official KNHANES website [25]. CRP in the present study was measured using Tina-quant C-Reactive Protein IV reagent kits, which differ from the CRP reagents used in KNHANES 2022 and 2023.

Evaluation of publicly available data

After identifying commonly associated factors based on the review of various laboratory test results, we further evaluated these factors using three publicly available datasets: the KNHANES, 2011 - 2023 [25,26], the Korean National Health Insurance Service (NHIS) database 2023 [5,26,27], and the United States (US) NHANES, 2015 - 2020 [28]. The NHIS database included only a limited set of clinical and laboratory variables. Available variables from NHIS included gender, age, height, weight, blood pressure, fasting blood glucose, total cholesterol, HDL-C, triglycerides, hemoglobin, urine protein (measured by dipstick test), selected liver chemistries (AST, ALT, and GGT), and self-reported history of smoking and alcohol consumption [27].

RESULTS

Baseline characteristics

During the one-year study period, a total of 1,022,234 specimens were tested for HDL-C at GC Labs, submitted from local clinics and hospitals. Among these, 147 specimens (0.015%) showed extremely low HDL-C levels (< 10 mg/dL). Out of these, 22 specimens were excluded because they contained only HDL-C, only lipid tests, or only HbA1c and lipid tests, without sufficient additional laboratory data to indirectly assess specimen status. As each specimen was associated with a different combination of test items, the evaluation was based on the subset of results available per specimen. Ultimately, 125 specimens (0.012% of the total) from 114 individuals were included in the final analysis. The subjects had a mean age of 60.1 years (interquartile range, 47.9 - 69.1 years) and consisted of 84 men (67.2%) and 29 women (23.2%).

Among these 125 specimens, 110 (88.0%) had both triglyceride and total cholesterol results available. Four specimens (3.2%) lacked triglyceride results but had total cholesterol values, all of which were within the desirable range (< 200 mg/dL). Eleven specimens (8.8%) had triglyceride results without accompanying total cholesterol measurements, with triglyceride levels ranging from 70 mg/dL to > 4,425 mg/dL).

Simultaneously measured lipid test results

Among the 125 specimens, 42 (33.6%) showed very high triglyceride levels (≥ 500 mg/dL), out of which 32 (76.2%) also had high total cholesterol levels (≥ 240 mg/dL). When applying the upper limit of the analytical measurement interval for triglycerides (> 885 mg/dL), 33 specimens were identified as exceeding this threshold. Among them, 31 had available total cholesterol measurements, and 29 (93.5%) had levels ≥ 240 mg/dL. The remaining two specimens had total cholesterol levels of 125 mg/dL and 224 mg/dL, respectively. On the other hand, among the 125 specimens, 24 (19.2%) had normal triglyceride levels (< 150 mg/dL). Out of these,

Table 1. Concurrent findings in specimens with extremely low HDL-C (< 10 mg/dL) across study and public datasets.

Category	Criteria for specimen findings	Possible clinical significance	Specimen number and prevalence			
			This study (n = 1,022,234)	KNHANES 2011 - 2023 (n = 80,891)	NHIS 2023 (n = 338,606)	NHANES 2015 - 2020 (n = 24,822)
Extremely low HDL-C	HDL-C < 10 mg/dL	Review for possible artifact or spurious HDL-C result	147 (0.015%) [*] 125 (0.012%) [†]	3 (0.004%)	15 (0.004%)	2 (0.008%) [*] 2 (0.009%) [‡]
Hypertriglyceridemia (very high)	Triglyceride ≥ 500 mg/dL [§]	Possible chylomicrons, endogenous glycerol, lipemia, or other interference	42 (33.6%)	3 (100.0%)	1 (6.7%)	0 (0.0%)
Hypercholesterolemia	Total cholesterol ≥ 240 mg/dL [§]	Suggests abnormal lipid profile	35 (28.0%)	1 (33.3%)	3 (20.0%)	0 (0.0%)
Abnormal liver chemistries	At least two abnormal liver chemistries [‖]	Liver disease may affect lipid test reliability	71 (56.8%)	3 (100.0%)	8 (53.3%)	1 (50.0%)
Elevated CRP	CRP ≥ 0.5 mg/dL	Inflammation may alter lipid levels	25 (20.0%)	1 (33.3%)	Not available	0 (0.0%)
Visual abnormality	Grossly lipemic appearance	Potential analytical interference caused by specimen turbidity	10 (8.0%)	Not available	Not available	Not available
Cold agglutinin	RBC agglutination observed on PB smear	Cold agglutinin may cause analytical interference	2 (1.6%)	Not available	Not available	Not available
Suspected dilutional effects, multi-analyte assay interference, or delayed specimen processing	Spuriously low or high values in three or more concurrently tested analytes, or a potassium concentration > 6.0 mmol/L	Potentially inaccurate results caused by improper specimen collection or handling	15 (12.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Suspected paraproteinemia or other sources of interference	Total serum protein > 8.6 g/dL & a reversed A/G ratio	Paraproteins may interfere with lipid assays	1 (0.8%)	Not available	Not available	0 (0.0%)
Decreased kidney function	eGFR < 60 mL/minute/ 1.73 m^2 (from serum creatinine)	CKD stage ≥ 3, with potential sources of analytical interference arising from disease management	39 (31.2%)	0 (0.0%)	1 (6.7%)	0 (0.0%)
Anemia	Hemoglobin < 11.0 g/dL in women and < 12.0 g/dL in men	Possible interfering factors during the management of anemia	58 (46.4%)	1 (33.3%)	0 (0.0%)	0 (0.0%)

Table 1. Concurrent findings in specimens with extremely low HDL-C (< 10 mg/dL) across study and public datasets (continued).

Category	Criteria for specimen findings	Possible clinical significance	Specimen number and prevalence			
			This study (n = 1,022,234)	KNHANES 2011 - 2023 (n = 80,891)	NHIS 2023 (n = 338,606)	NHANES 2015 - 2020 (n = 24,822)
Diabetes	HbA1c ≥ 6.5%, glucose ≥ 200 mg/dL, or a documented history of diabetes diagnosis	Potential sources of interference associated with anemia management	33 (26.4%)	2 (66.7%)	1 (6.7%)	1 (50.0%)
Extremely low HDL-C without other abnormalities	No additional abnormalities were observed in the available laboratory and clinical data	Other possible sources of interference (e.g. medications, antibodies) or primary genetic causes	1 (0.8%)	0 (0.0%)	2 (13.3%)	0 (0.0%)

The total prevalence exceeds 100%, because some specimens exhibited multiple findings across categories.
*** To screen for extremely low HDL-C, all HDL-C test results were included in the denominator.**
† To assess the prevalence of associated findings in the specimens, n = 125 (specimens with extremely low HDL-C and available additional laboratory test results) was used as the denominator in this study.
‡ To assess the prevalence of associated findings in the specimens, n = 21,724 was used as the denominator for NHANES 2015 - 2020, after excluding specimens without concurrently measured laboratory test results.
§ Very high triglyceride and high total cholesterol levels were defined according to the NCEP ATP III criteria.
‖ Liver chemistries including AST, ALT, GGT, ALP, total bilirubin, and direct bilirubin.
A/G ratio albumin to globulin ratio, ALP alkaline phosphatase, ALT alanine transaminase, AST aspartate aminotransferase, CKD chronic kidney disease, CRP C-reactive protein, GGT gamma-glutamyl transferase, HDL-C high-density lipoprotein cholesterol, NCEP ATP the National Cholesterol Education Program Adult Treatment Panel, RBC red blood cell, PB peripheral blood.

21 had available total cholesterol results, and 20 (95.2%) showed normal total cholesterol levels. When applying the upper analytical limit for total cholesterol (> 800 mg/dL), 11 specimens (8.8%) were identified with extremely high total cholesterol levels (range: 813 - 1,550 mg/dL). All 11 specimens also had extremely elevated triglyceride levels (> 4,425 mg/dL), and among them, 4 specimens (36.4%) showed grossly lipemic appearance. Figure 1 summarizes the triglyceride and total cholesterol groupings based on the NCEP ATP III criteria for the 110 specimens with both test results available.

Simultaneously measured laboratory test results and associated conditions

Among the 125 specimens, 71 (56.8%) showed abnormal liver chemistries, 39 (31.2%) showed decreased kidney function (eGFR < 60 mL/minute/1.73 m²), 25 (20.0%) had elevated C-reactive protein (CRP ≥ 0.5 mg/dL), and 15 (12.0%) showed multiple extreme abnormalities in electrolytes, total protein, albumin, and/or uric acid levels, suggestive of compromised specimen quality prior to or during collection. Although only 12 specimens were tested for lactate dehydrogenase (LDH), all showed elevated LDH levels (range: 226 - 859 U/L; reference interval: 135 - 225 U/L). Among the 20 specimens without any of the abovementioned abnormalities, the most common findings were a history of diabetes (10 specimens, 50%) and anemia (6 specimens, 30%).

Among the 20 specimens with normal triglyceride and total cholesterol levels, common findings included decreased kidney function (12 specimens, 60%), anemia (8 specimens, 40%), and abnormal liver chemistries (7 specimens, 35%), followed by elevated CRP (4 specimens, 20%), diabetes (2 specimens, 10%), and suspected specimen handling issues (2 specimens, 10%).

Out of the 125 specimens, 4 (3.2%) did not show any of the following: gross lipemia, presence of cold agglutinin, abnormal liver chemistries, decreased kidney function, elevated CRP, extreme abnormalities in other analytes, diabetes, or anemia. Among these four, one had hypercalcemia (11.4 mg/dL; reference interval: 8.6 - 10.0 mg/dL), one had thrombocytopenia (73 × 10³/μL), and one had a normal C-peptide level (2.9 ng/mL; reference interval: 1.1 - 4.4 ng/mL), which might suggest a history of diabetes. The remaining specimen - accounting for 0.8% of the 125 specimens and 0.0001% of all 1,022,234 specimens - was from a 57-year-old woman with normal triglyceride and total cholesterol levels, a

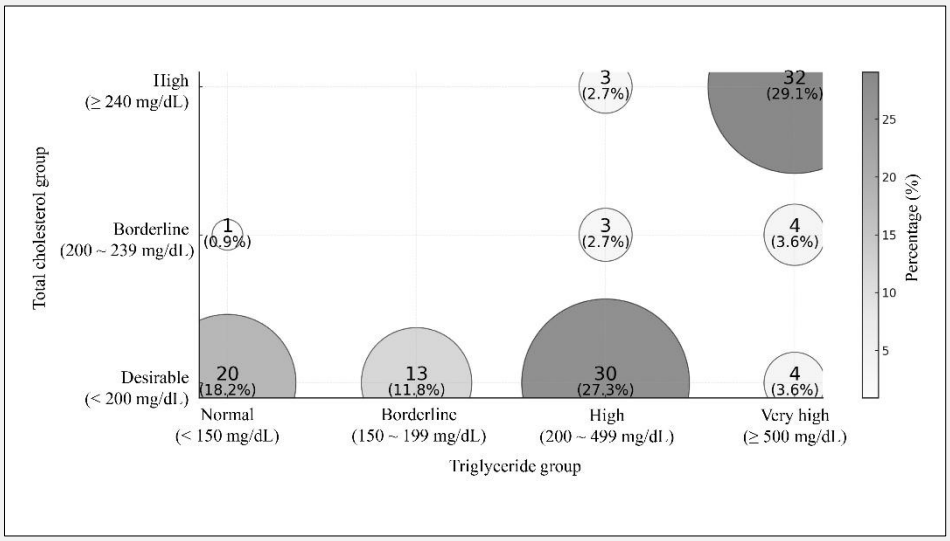

Figure 1. Distribution of specimens by combined triglyceride and total cholesterol categories using bubble plot visualization (n = 110).

Bubble size represents the number of specimens in each triglyceride/total cholesterol group based on the NCEP ATP III criteria, while color intensity indicates the relative percentage. Each bubble is labeled with the specimen count (n) and its corresponding percentage (%).

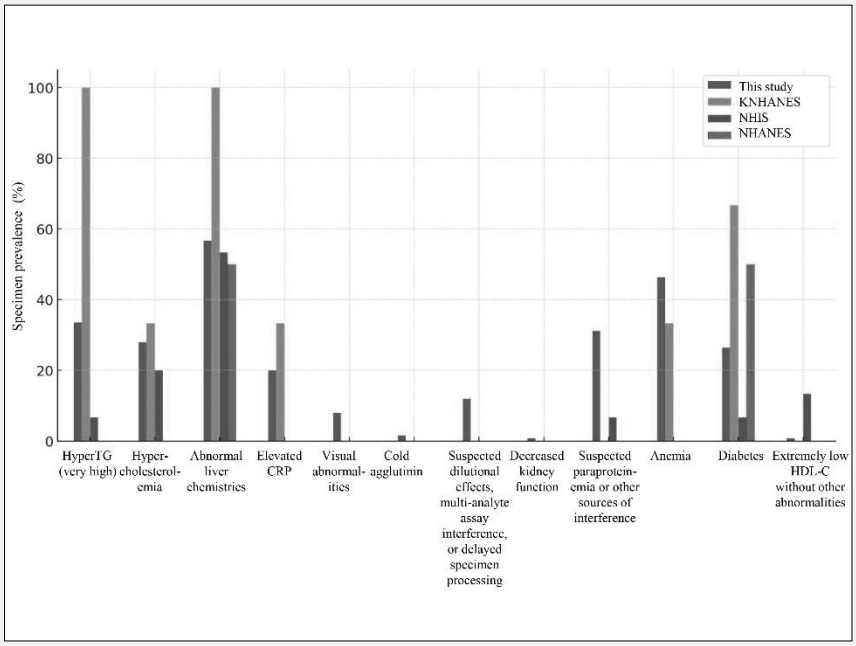

Figure 2. Prevalence of concurrent laboratory findings in specimens with extremely low HDL-C (<10 mg/dL).

Very high triglyceride and high total cholesterol levels were defined according to the NCEP ATP III criteria.
CRP C-reactive protein, HDL-C high-density lipoprotein cholesterol, KNHANES Korea National Health and Nutrition Examination Survey, NCEP ATP the National Cholesterol Education Program Adult Treatment Panel, NHANES United States National Health and Nutrition Examination Survey, NHIS National Health Insurance Service, TG triglycerides.

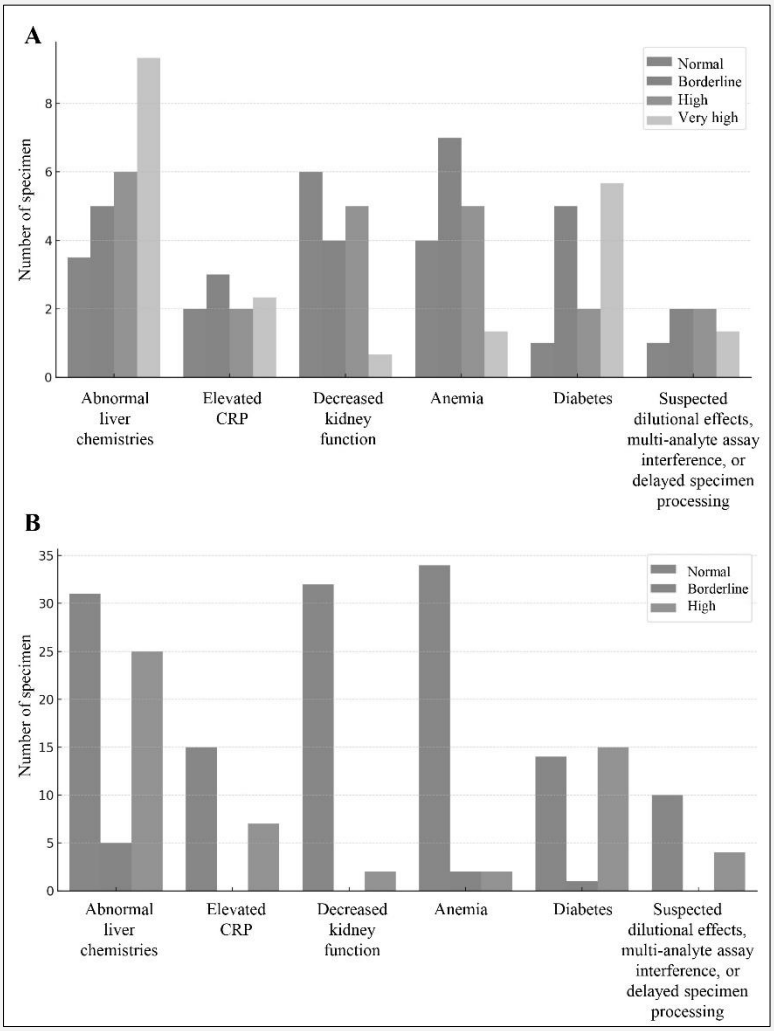

Figure 3. Number of specimen with concurrent laboratory findings among those with extremely low HDL-C (< 10 mg/dL), stratified by triglyceride (A) and total cholesterol (B) result groups.

serum glucose level of 132 mg/dL, a normal HbA1c level (5.2%), and no other abnormal findings meeting the predefined laboratory abnormality criteria. Figure 2 summarizes the characteristics of specimens with extremely low HDL-C, while Figure 3 presents these characteristics stratified by triglyceride and total cholesterol result groups.

Extremely low HDL-C specimens in publicly available data sources

Among 80,891 HDL-C test results from KNHANES 2011 - 2023, three specimens (0.004%), tested in 2016, 2018, and 2023, showed extremely low HDL-C levels (< 10 mg/dL). Two were male and one was a female subject, aged between 30 and 62 years. All three had very high triglyceride levels (ranging from 605 to 3,367 mg/dL), while their total cholesterol levels varied (171 - 403 mg/dL). All had elevated liver chemistries and diabetes; two had anemia, and one had elevated CRP.

Among 338,606 HDL-C results from the NHIS database in 2023, 15 individuals (0.004%) had extremely low HDL-C levels (< 10 mg/dL). Out of these, nine were male and six were female. Only one subject had both very high triglyceride (2,472 mg/dL) and high total cholesterol (432 mg/dL). Triglyceride levels among these 15 subjects ranged from 35 to 2,472 mg/dL, and total cholesterol levels ranged from 120 to 2,305 mg/dL. Two subjects had extremely high total cholesterol levels (1,863 mg/dL and 2,035 mg/dL, respectively), while the remaining 13 had variable total cholester-

ol levels (120 - 238 mg/dL). Among all 15, eight (53.3%) had abnormal liver chemistries. Two subjects (13.3% of the 15 subjects; 0.0006% of the 338,606 total) did not show any findings suggestive of associated conditions, such as abnormal liver chemistries, decreased eGFR based on serum creatinine, elevated fasting glucose, anemia, proteinuria, or hypertension.

In the US NHANES dataset, data are released in 2-year cycles for each phase, except for the 2017 - 2020 period, which was combined due to the COVID-19 pandemic. During phases I (2015 - 2016), J (2017 - 2018), and P (2017 - 2020), a total of 24,822 subjects were tested for HDL-C. Among these, 21,724 subjects also had BIOPRO panel data, which included other clinical chemistry results. Out of this group, two subjects (0.009%) had extremely low HDL-C levels (< 10 mg/dL). One subject had high triglycerides (276 mg/dL), normal total cholesterol (161 mg/dL), and liver disease. The other was a 76-year-old woman with diabetes and hypertension who had elevated CRP, borderline-high triglycerides (230 mg/dL), and normal total cholesterol (105 mg/dL). Table 1 summarizes the prevalence and clinical characteristics of specimens with extremely low HDL-C levels across the three public datasets.

DISCUSSION

This study identified and characterized clinical specimens with markedly low HDL-C levels, defined as < 10 mg/dL and considered as rare events in clinical laboratories, over a one-year period at a referral laboratory serving local clinics and hospitals nationwide. Public datasets representing the general populations of Korea and the United States were also analyzed for comparison.

While low HDL-C is a well-established risk factor for cardiovascular disease, extremely low levels are uncommon and may be attributable to pre-analytical, analytical, or post-analytical factors [6,18]. In the present study, approximately 0.01% of specimens (1 in 10,000) had HDL-C levels < 10 mg/dL, with a similar prevalence observed across all study populations. Across all four datasets, approximately half or more of the specimens with extremely low HDL-C had abnormal liver chemistries. This aligns with the well-documented observation that lipid test results may be unreliable in the presence of liver dysfunction [2,6,11]. Other commonly observed findings associated with extremely low HDL-C in this study included decreased kidney function, inflammation (elevated CRP), anemia, and diabetes. The proportion of these findings is comparable to those reported in previous studies using cutoffs of < 20 mg/dL or < 15 mg/dL for extremely low HDL-C [11,17]. The presence of very high triglyceride levels (≥ 500 mg/dL) in many of these specimens supports previous observations of an inverse correlation between HDL-C and triglyceride-rich lipoproteins [6,11,17]. These findings may suggest chylomicronemia, elevated endogenous unesterified glycerol, or lipemic interference - particularly in non-fasting specimens [6,11,17]. Furthermore, this study identified possible specimen collection and handling issues, highlighting the importance of the pre-analytical phase in ensuring the reliability of test results. Implementing reflexive review protocols or automated flagging systems may improve the reliability of extreme value interpretation and support better clinical decision-making [15].

Meanwhile, a small number of specimens in this study exhibited isolated, extremely low HDL-C values with otherwise unremarkable test results within reference intervals (1 in 166,667 in NHIS and 1 in 1,000,000 overall). These cases may represent true biological extremes, rare genetic conditions (e.g. mutations in *ABCA1*, *LCAT*, or *APOA1*), or unrecognized analytical errors that could not be detected through the limited laboratory tests available in this study. Potential interferences from nutritional supplements, herbal remedies, medications, or comorbidities may also have contributed to these findings [6,9,18]. More detailed clinical information is needed to clarify the clinical significance of these observations.

Our findings underscore the value of contextual laboratory data review in distinguishing physiologic, pathologic, and artifactual causes of extreme HDL-C values [15]. In routine clinical practice, isolated abnormal results should prompt reflexive review of concurrently ordered tests and, when necessary, communication with the ordering physician [15,18].

This study has several limitations. First, as hemolysis, icterus, and lipemia (HIL) indices were not available during the study period, identification of potential interferences relied on indirect patterns across multiple test results. This may have reduced the sensitivity and specificity of interference detection. Second, the study was based solely on laboratory data without access to detailed clinical records or patient histories, limiting the ability to correlate findings with underlying diseases such as genetic lipid disorders or hepatic dysfunction. Third, because the data were obtained retrospectively from outpatient clinics and hospitals in South Korea, the generalizability of our findings to other populations, inpatients, or different laboratory settings may be limited.

In conclusion, extremely low HDL-C values in clinical specimens are rare but are frequently associated with identifiable biochemical abnormalities or analytical interference. A structured approach to reviewing concurrent laboratory results can aid in differentiating true pathological findings from preanalytical or analytical errors, and may ultimately enhance diagnostic accuracy, reduce misinterpretation, and improve overall quality assurance in clinical laboratory practice.

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Declaration of Interest:
The authors declare that they have no conflicts of interest.

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