

## Original Article

# Clinical features and outcomes of severe, very severe, and extreme hypertriglyceridemia in a regional health service

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**KEYWORDS:**

Hypertriglyceridemia;  
Pancreatitis;  
Myocardial infarction;  
Stroke;  
Mortality

**BACKGROUND:** Comprehensive data on severe hypertriglyceridemia (HTG) in the general population setting are limited and of importance due to the increase in metabolic risk factors and novel therapies under development.

**OBJECTIVE:** To investigate contributing causes and outcomes of severe to extreme HTG.

**METHODS:** Regional database retrospectively analyzed for subjects with severe HTG. Adverse outcomes were investigated in correlation to HTG severity, with follow-up initiating at first documentation of HTG > 1000 mg/dL.

**RESULTS:** A total of 3091 subjects with severe (peak triglycerides 1000–1999 mg/dL;  $n = 2590$ ), very severe (2000–2999 mg/dL;  $n = 369$ ), and extreme ( $\geq 3000$  mg/dL;  $n = 132$ ) HTG were identified. Mean age was  $48 \pm 12$  years; 73% males. Obesity (48%) and diabetes (62%) were main contributing factors. During follow-up (median 101 months), 4.7% subjects had pancreatitis, 4.7% myocardial infarction, and 6% stroke. Compared with severe HTG, the multivariate-adjusted hazard ratio for pancreatitis was 3.22 (95% confidence interval 2.21–4.70) for individuals with very severe HTG and 5.55 (3.53–8.71) for those with extreme HTG,  $P < .0001$ . In contrast, the extent of HTG severity at these levels was not associated with worse cardiovascular outcomes or death. Most subjects (81%) achieved triglyceride levels <500 mg/dL, associated with lower risk for developing pancreatitis but not myocardial infarction or stroke.

**CONCLUSIONS:** Severity of HTG is closely related to cardiometabolic conditions, with a stepwise increase in the risk for pancreatitis, particularly if not attaining reduced triglyceride levels during the follow-up. In contrast, whereas mild-to-moderate HTG is a known established cardiovascular risk factor, very severe and extreme HTG may not further increase the risk for myocardial infarction, stroke, or mortality.

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## Introduction

Hypertriglyceridemia (HTG) is closely related to obesity, sedentary lifestyle, and insulin resistance, features of the metabolic syndrome.<sup>1</sup> Mild-to-moderate HTG is considered a common risk factor for atherosclerotic cardiovascular disease (ASCVD), reflecting increased levels of

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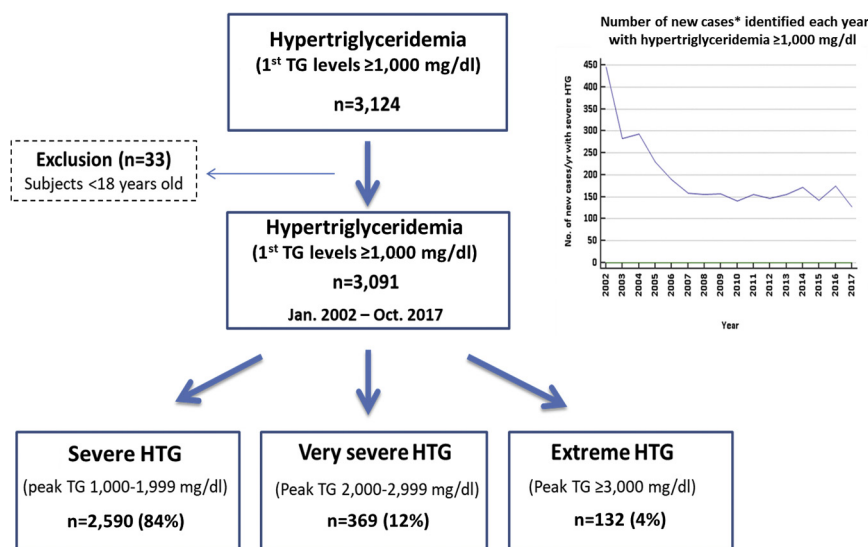
triglyceride-rich lipoproteins, evolving into remnant particles that contain high concentration of cholesterol, which may contribute to atherosclerotic plaque development.<sup>2,3</sup> Elevated triglycerides are also associated with increased risk for acute pancreatitis, particularly observed in severe HTG.<sup>4</sup> Different triglyceride cutoffs were suggested over the years by professional taskforces and national societies for defining “severe HTG”.<sup>1</sup> The Endocrine Society clinical practice guideline proposed defining fasting triglyceride levels between 1000 and 1999 mg/dL as severe HTG and above 2000 mg/dL as very severe HTG to emphasize the significant increase in the risk for acute pancreatitis associated with these levels.<sup>5</sup> Although recent studies have investigated the association and predictive value of mild-to-moderate HTG with adverse events, comprehensive data on the prevalence, characteristics, and outcomes of severe and extreme HTG are lacking.<sup>6,7</sup> It is also unclear whether the presence of mild-to-moderate HTG as a consequence of treated severe HTG is an independent risk factor for cardiovascular disease, and whether it is associated with lower rates of pancreatitis. Furthermore, clarification of the features and outcomes of severe HTG is of importance in light of the population increase in the prevalence of metabolic risk factors and the novel therapies for HTG, which are currently under development and may be primarily designated to this population with severe HTG.<sup>8</sup>

In the present study, we aimed to analyze the characteristics and risk factors contributing to severe HTG in the setting of the general population and investigate adverse outcomes including acute pancreatitis, myocardial infarction, stroke, and all-cause death in correlation to the severity degree of HTG, categorized as severe, very severe, or extreme HTG. Moreover, we wished to examine whether successfully reducing triglyceride levels is associated with better outcomes.

## Materials and methods

### Study population

A regional laboratory database (Haifa and Western Galilee, Israel) of Clalit Health Services, the largest health maintenance organization in Israel, was screened retrospectively between the years January, 2002 and October, 2017 to identify insured individuals with marked HTG  $\geq 1000$  mg/dL. Study population flowchart is presented in Figure 1. The number of subjects with available lipid profile sampled each year ranged from 192,707 in the year 2002 to 312,623 in the year 2017. The yearly incidence of HTG  $\geq 1000$  mg/dL ranged from 0.093% to 0.254% (number of individuals with triglyceride levels  $>1000$  mg/dL out of the population performing blood test for lipid panel at the same year). Overall, 3124 subjects with triglyceride values  $\geq 1000$  mg/dL were identified. Patients under the age 18 years ( $n = 33$ ) were excluded from final analysis. Date of the first triglyceride value  $\geq 1000$  mg/dL during study period was considered as the initial date of the follow-up. In addition, peak (highest triglyceride levels documented in patient’s history in the computerized laboratory database) and most recent triglyceride levels of each subject were documented. Individuals were classified according to 3 categories of peak triglyceride levels: severe (peak triglyceride levels 1000–1999 mg/dL), very severe (2000–2999 mg/dL), and extreme ( $\geq 3000$  mg/dL). Lipid profiles were measured in a centralized district laboratory with blood tests customary taken after prolonged fasting of 12 hours. Triglyceride measurement was performed by homogeneous enzymatic assay method.



**Figure 1** Study population flowchart. Number of new cases of hypertriglyceridemia  $>1000$  mg/dL identified each year out of the total number of individuals with triglyceride values available each year in the computerized database (mean number of subjects searched each year was 279,651). Only the first episode of hypertriglyceridemia in each patient was included. TG, triglycerides; HTG, hypertriglyceridemia.

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