somewhat different

Underwriting LFTs

Key Points and Summary of Insurance Applicant Data

Cliff Titcomb, MD
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5 Tests Commonly Known as Liver Function Tests

- Alanine Aminotransferase (ALT, SGPT)
- Aspartate Aminotransferase (AST, SGOT)
- Gamma-Glutamyltransferase (GGT)
- Alkaline Phosphatase (ALP)
- Bilirubin

- Only problem
  - They are not specific to the liver
  - They don’t measure liver function

LFTs Actually Measure:

- Hepatocellular injury (ALT, AST)
- Interruption of bile flow or cholestasis (ALP, GGT)
- Processing of hemoglobin (bilirubin)
  - Actually comes closest to measuring a functional activity of the liver

True Measures of Liver Function

- Serum albumin – synthesized in the liver
- Serum cholesterol – synthesized in the liver
- Prothrombin time
  - Measures coagulation factors produced in the liver

Hepatocellular Enzymes – ALT, AST

- Found within the liver cells
- Released into the circulation when cells are damaged or destroyed
- Differ in their specificity for the liver and distribution within the hepatocytes

ALT

- Found in a variety of tissues
  - Kidney, lung, pancreas, RBCs, skeletal muscle
- Concentration is by far the highest in the liver
- Considered relatively specific for the liver
- Located only in the cytoplasm of the cell

AST

- Also found in many tissues
  - Heart, brain, skeletal muscle, kidney
- More evenly distributed than ALT
- Less specific for the liver
- Found in both the hepatocyte mitochondria (80%) and cytoplasm (20%)
- May be found as a macroenzyme
  - Polymerization with other serum proteins
  - Larger than normal molecule
  - Can lead to false positive elevations

Levels and Pathology

- Type of damage affects degree of elevation
  - Apoptosis - programmed cell death
    - Decreased cell activity before death
    - Common form of pathology in hepatitis C
      - Reason for poor correlation between degree of elevation and severity of injury
- Damage may occur more extensively in one portion of cell
  - Alcohol affects mitochondria more than cytoplasm
  - Reason for greater elevation of AST

Levels and Pathology

- Toxic agent may affect substrate for synthesis of transaminases differently
  - Pyridoxine (vitamin B_6) is needed to synthesize ALT
  - Alcohol reduces pyridoxine and amount of ALT production
    - Combined with mitochondria effects leads to AST > ALT
- Need viable hepatocytes to produce enzymes
  - With severe cirrhosis there are not enough viable liver cells left to produce significant transaminase elevations

Alkaline Phosphatase

- 80% originates from bone or liver – normal individuals
- Most of the rest from the intestine
- May be increased in normal situations
  - Pregnant women (placental origin)
  - Growing children and adolescents (bone)
  - Blood group B or O (intestinal - after fatty meal)
  - Age (increases between 40-65, especially in women)

Pathologic Elevations ALP – Site of Obstruction

- Diffusely in liver – hepatitis or drug reactions
- Locally in liver – tumors, granulomatous disease
- Extrahepatic – gallstones, tumors
- Isolated elevations < 1.5 x normal usually resolve spontaneously
- Persistent elevations > 1.5 x normal suggest more severe pathology

GGT

- Most sensitive marker for biliary tract disease
- Problem is poor specificity
  - Found in a variety of tissues
    - Heart, brain, pancreas, kidney, spleen, seminal vesicles
  - Induced by a variety of agents
    - Alcohol, barbiturates, phenytoin
  - Increases with age, male sex and obesity
- Involved in the metabolism of glutathione
- Associated with cardiovascular disease
  - Indicator of oxidative stress
  - Associated with markers of inflammation
  - Correlated with traditional cardiovascular risk factors
  - May be directly involved in the formation of coronary plaques

Bilirubin

- Results from enzymatic breakdown of heme
- Processed in liver for excretion in bile
- Conjugated with glucuronic acid to make water soluble
  - Direct bilirubin = conjugated
  - Indirect bilirubin = unconjugated

Elevations of Bilirubin

- Most common is indirect – values usually < 3 mg/dl (51.3 umol/L)
  - Gilbert's disease -benign defect in conjugating enzymes
  - Hemolysis
    - Overwhelms the liver with too much bilirubin to be processed
- Direct hyperbilirubinemia = significant liver disease
  - Indicates loss of at least half of functional capacity

Composite Risk of a Group

- Sometimes a lab test or other factor does not point to a specific diagnosis
- Indicates a group of individuals with multiple different risks
- Examples:
  - Liver function tests
  - PSA readings
- Underwriters are rating the risk of the group with the abnormality or finding
- Individuals within the group may or may not have an increased risk
- It is the composite risk of the group that matters

Composite Risk of a Group

- Subcategories or diagnoses making up the group
- Example: liver function tests
  - Alcohol abuse
  - Hepatitis B
  - Hepatitis C
  - Fatty liver
  - Others
- Relative risk for each of the diagnoses
- Calculate the composite risk of the group
  - (% diagnosis 1 x RR) + (% diagnosis 2 x RR) + (% diagnosis 3 x RR) etc.

Composite Risk of a Group

LFTs as an Example

Diagnosis	Percentage	Relative Risk	Composite RR
Alcohol	25%	3	0.75
Hepatitis B	3%	3	0.09
Hepatitis C	15%	2.5	0.38
Others	57%	1.3	0.74
Total	100%		1.96

Composite Risk of a Group

- Key assumption – the distribution of diagnoses depends on the pattern and degree of enzyme elevation
- Different patterns have different distributions and different risks
- Value of reflex tests also depends on the pattern and distribution
- Key patterns of importance
  - Single enzyme elevations (ALT, AST, GGT alone)
  - Two enzymes elevated (ALT+AST, GGT+ALT, GGT+AST)
  - All three enzymes elevated (ALT+AST+GGT)
  - Alkaline phosphatase alone
  - Alkaline phosphatase combined with other enzymes
  - Bilirubin alone
  - Bilirubin combined with other enzymes

LFT Summary

- Isolated ALT elevations higher than 2 x normal are very unusual
  - Represent only 0.041% of insurance applicants tested
- Very low rate for positive reflex tests with isolated ALT elevations
  - CDT < 2%, hepatitis C antibody < 1%. Hepatitis B antigen < 1%
- Isolated elevated ALT levels show little to no mortality in the US – especially insurance applicant population
- Low normal ALT values (<10 UL) show increased mortality
  - RR in the 1.25-1.50 range
  - Seen in insurance applicants and clinical literature
  - Cause is unclear but may be due to sarcopenia (reduced muscle mass, frailty), reduced BMI, nutritional deficiency, especially pyridoxine (vitamin B6)
- Isolated elevated ALT levels may show increased mortality risk in Asian populations
  - Possibly related to endemic hepatitis B

LFT Summary

- Isolated AST elevations are often *not* related to the liver
  - Frequently of muscle origin
    - Confirmed by concurrent CPK or aldolase elevations
  - Macroenzymes
    - Larger than normal molecules measured as higher levels by analyzers
- Reflex tests
  - CDT percentage is modestly higher than ALT, hepatitis B and C are about the same
- Mortality risk is mildly higher with elevated AST than elevated ALT
- Like ALT, a low normal AST (< 10 U/L) is associated with higher mortality
  - Relative risk in the 1.5-1.75 range (higher than that with ALT)
  - As with ALT the speculation is that it is a reflection of sarcopenia but cause is not known for certain

GGT

- Mortality risk of isolated elevations of GGT steadily rises with higher levels
  - Different than ALT and AST
- Major cause of death is cardiovascular disease
  - Risk of cancer death is increased but is much less than that seen with CV disease
  - Risk is not associated with liver disease as the cause of death in isolated GGT elevations
    - Liver biopsies do not show significant pathology
- Reflex test positive rates are low
  - CDT – 5% or less
    - Prevalence does not increase with higher levels of enzyme
  - Hepatitis C increases with level but max is less than 4%
  - Hepatitis B percentage that largely less than 1% to maximum of 2%

Two Enzymes Elevated

- ALT+AST (46%), GGT+ALT (33%), GGT+AST (21%)
- Reflex test results vary by the pattern
  - CDT
    - More likely with GGT+AST – maximum 18%
    - Least likely with ALT+AST – maximum 4%
  - Hepatitis C
    - More likely with ALT+AST – maximum 13%
    - Least likely with GGT+ALT – maximum 8%
  - Hepatitis B
    - More likely with ALT+AST – maximum 4%
    - Least likely with the others – maximum 1%

Two Enzymes Elevated

- Mortality risk varies with the combination
- Highest risk with GGT+AST
  - By definition AST is higher than ALT for most situations
- Lowest risk is with ALT+AST
  - Speculation that improved treatments of hepatitis B and C have lowered the risk in this group
  - Exception - if the AST > ALT – risk is substantially increased
    - Indication for possible alcohol abuse (differential effects of alcohol on AST and ALT as noted previously)
    - Higher risk of fibrosis even if alcohol is not the cause of the elevations
    - Some studies suggest increased risk of cardiovascular disease as well
- Combination of GGT+ALT is intermediate between the other two

Three Enzymes Elevated

- CDT
  - Generally ranges in the 5-7% range as enzyme levels increase with maximum of 9%
  - As with other groups, positive rate does not clearly scale up with enzyme level
- Hepatitis C and B positive rates clearly scale up but with different maximums
  - Hepatitis C antibody maximum is 18%
  - Hepatitis B antibody maximum is 3% (US insurance applicant population)
- Mortality clearly increase as enzyme levels rise
- Overall risk higher with all three enzymes elevated

Effect of an Elevated HDL Cholesterol Level

- Probability of an elevated CDT level is increased
- Mortality risk varies with pattern of enzyme elevation
  - Little effect for single enzyme elevations and GGT+ALT
    - Question if the cardio-protective effect of an elevated HDL offsets the modest increase in alcohol related mortality with these patterns
  - Risk increases with ALT+AST, GGT+AST, GGT+ALT+AST

Alkaline Phosphatase and Bilirubin

- Alkaline phosphatase increases mortality risk modestly if elevated alone
- Mortality risk increases substantially if alkaline phosphatase is elevated in conjunction with other enzymes
- Little to no risk with an increase in bilirubin alone
  - Most often due to Gilbert's syndrome in an insurance environment
- Higher levels of bilirubin (> 2 x normal) increase risk when combined with other LFT abnormalities
  - However, variable depending on enzyme pattern and degree of elevation
  - If a significant marker for mortality – indicates actual impairment of liver function
- Low bilirubin levels (< 0.2 mg/dl or 3.42 umol/L) are associated with increased risk
  - Bilirubin has antioxidant and anti-inflammatory effects
  - Increased risk of cardiovascular disease is associated with low levels
  - Functionally a low bilirubin and high GGT have similar mechanisms for mortality outcomes

Serum Albumin

- Serum albumin is synthesized in the liver
- Low serum albumin is associated with increased risk even if LFTs are normal
- Mortality risk is increased significantly if reduced serum albumin is associated with abnormal LFTs
  - Risk is moderately higher if serum albumin is in the 3.5-3.9 mg/dl (35-39 g/L) range
  - Risk is extremely high if serum albumin is less than 3.5 mg/dl (35 g/L)

LFT – Green flags

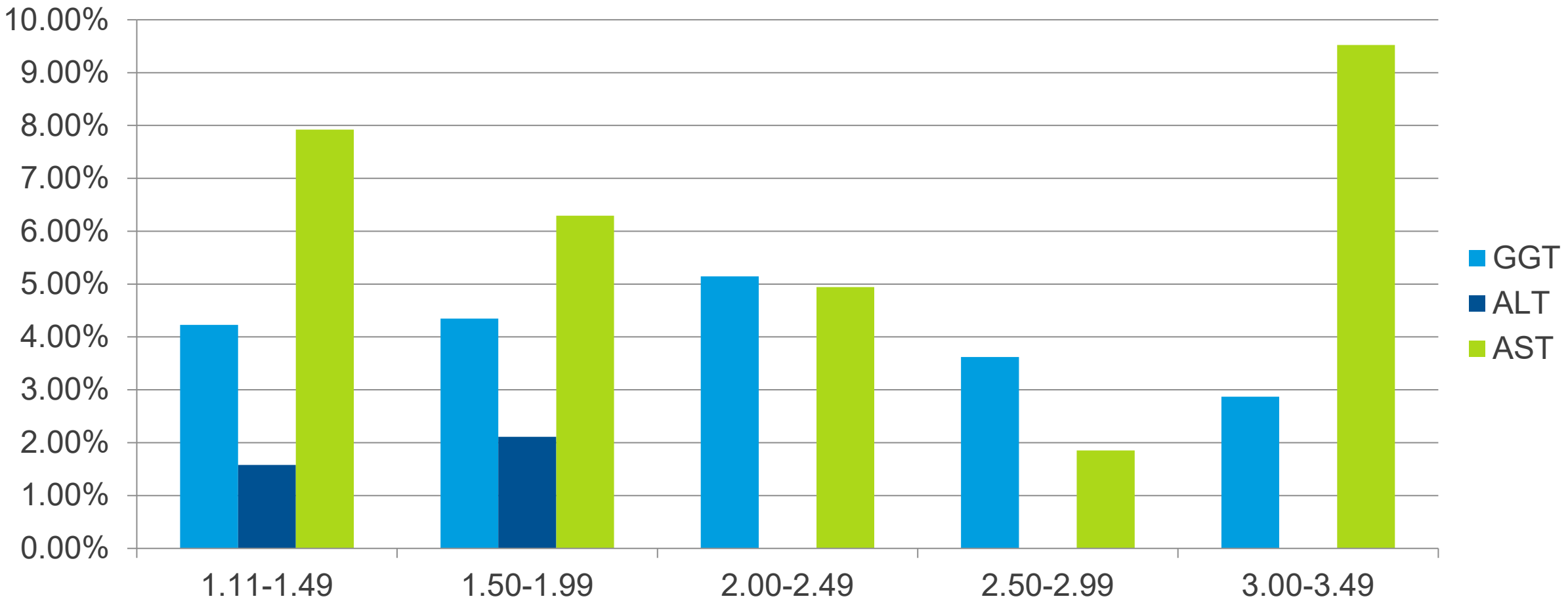
- Other non-invasive tests – the more are normal – the better the risk
  - Composite risk of the group is better the more serious illnesses can be excluded

- Tests to rule out underlying causes
  - Hepatitis C antibody – hepatitis C
  - Hepatitis B surface antigen – hepatitis B
  - CDT – alcohol (limited value)
  - Serum ferritin, iron saturation – hemochromatosis
  - ANA, anti-smooth muscle antibody – autoimmune hepatitis
  - Ceruloplasmin, copper levels – Wilson's disease
  - Alpha-1-antitrypsin – alpha-1-antitrypsin deficiency
  - Anti-mitochondrial antibody – primary biliary cirrhosis

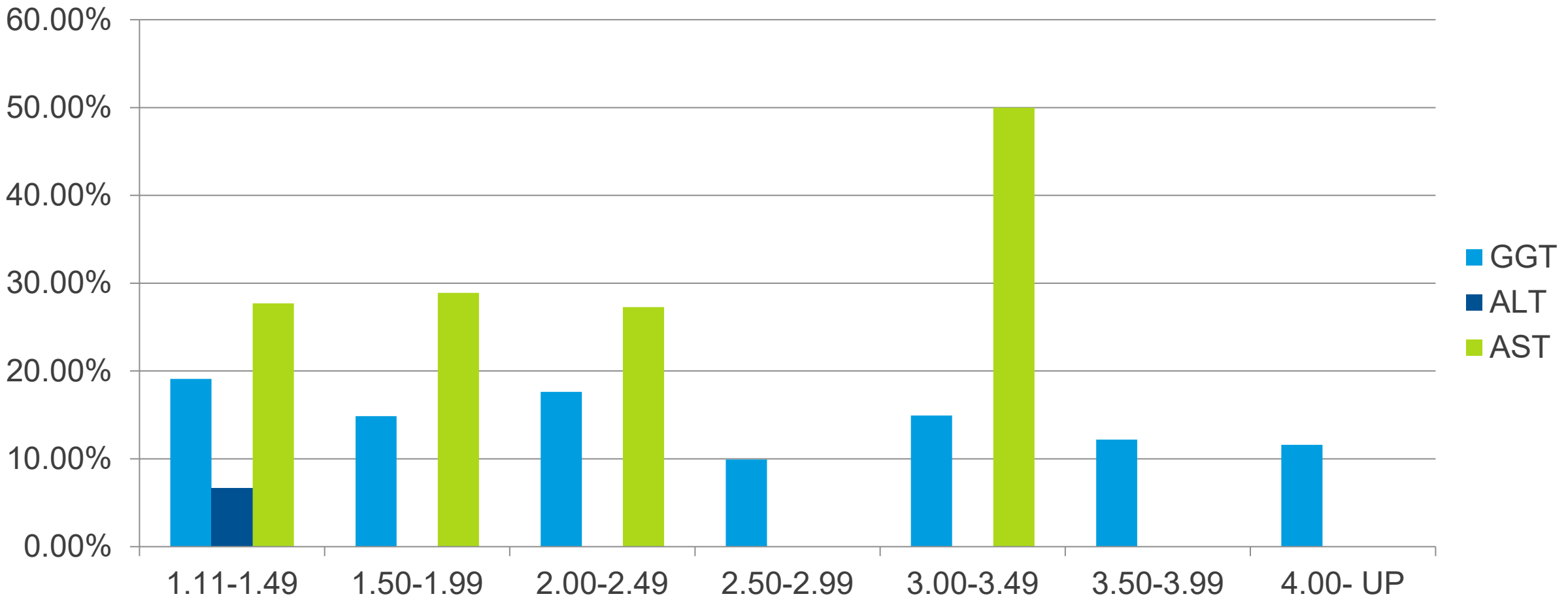
LFT – Red flags

- History of cancer
- AST:ALT ratio ≥ 1
  - Associated with alcohol
  - Indication of fibrosis or cirrhosis even if alcohol is not the cause for the elevations
- Indicators of reduced liver synthetic function
  - Low serum albumin
  - Low serum cholesterol
  - Elevated prothrombin time (INR)
- Abnormal alpha-fetoprotein (marker for hepatocellular cancer)
- Evidence of fibrosis on CT or MRI
- Abnormal non-invasive test for fibrosis
  - Fibrosure, Fibroscan

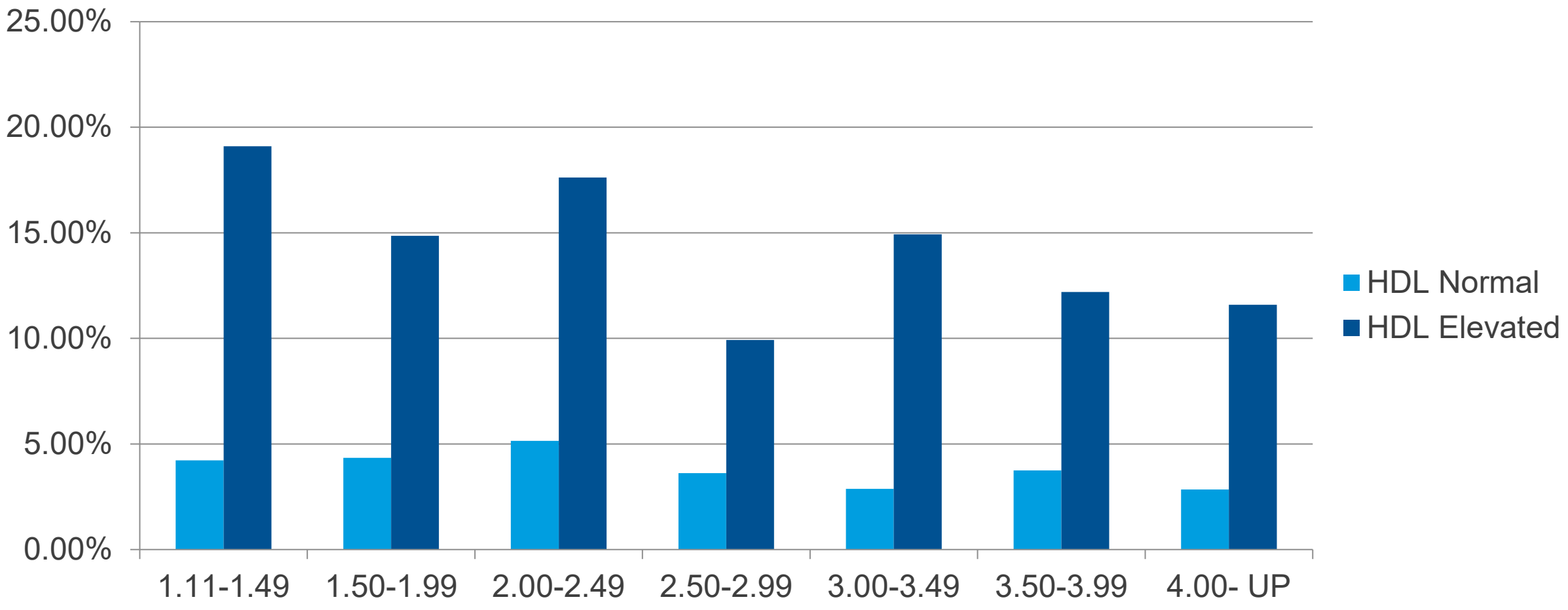
CDT Prevalence by Enzyme – Single Enzyme Elevated HDL Normal



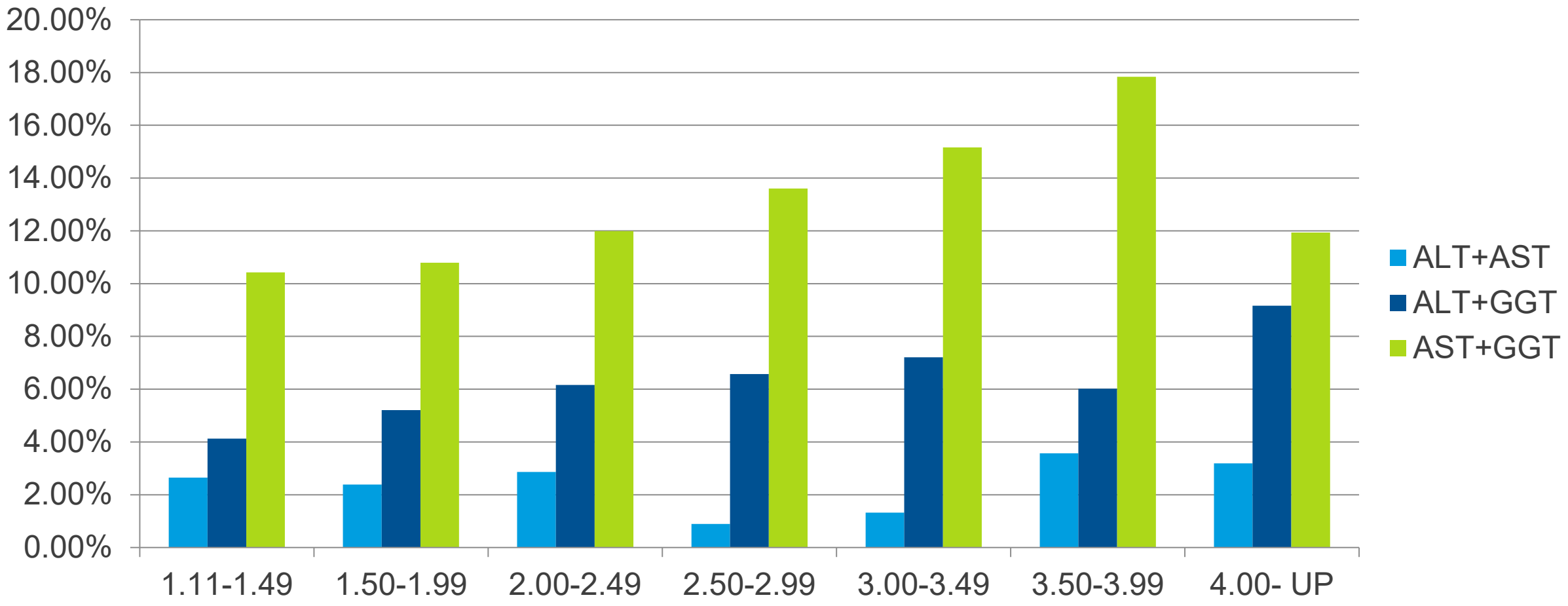
CDT Prevalence by Enzyme – Single Enzyme Elevated
HDL Elevated



CDT Prevalence by Enzyme – Only GGT Elevated



CDT Prevalence by Enzyme – Two Enzymes Elevated HDL Normal



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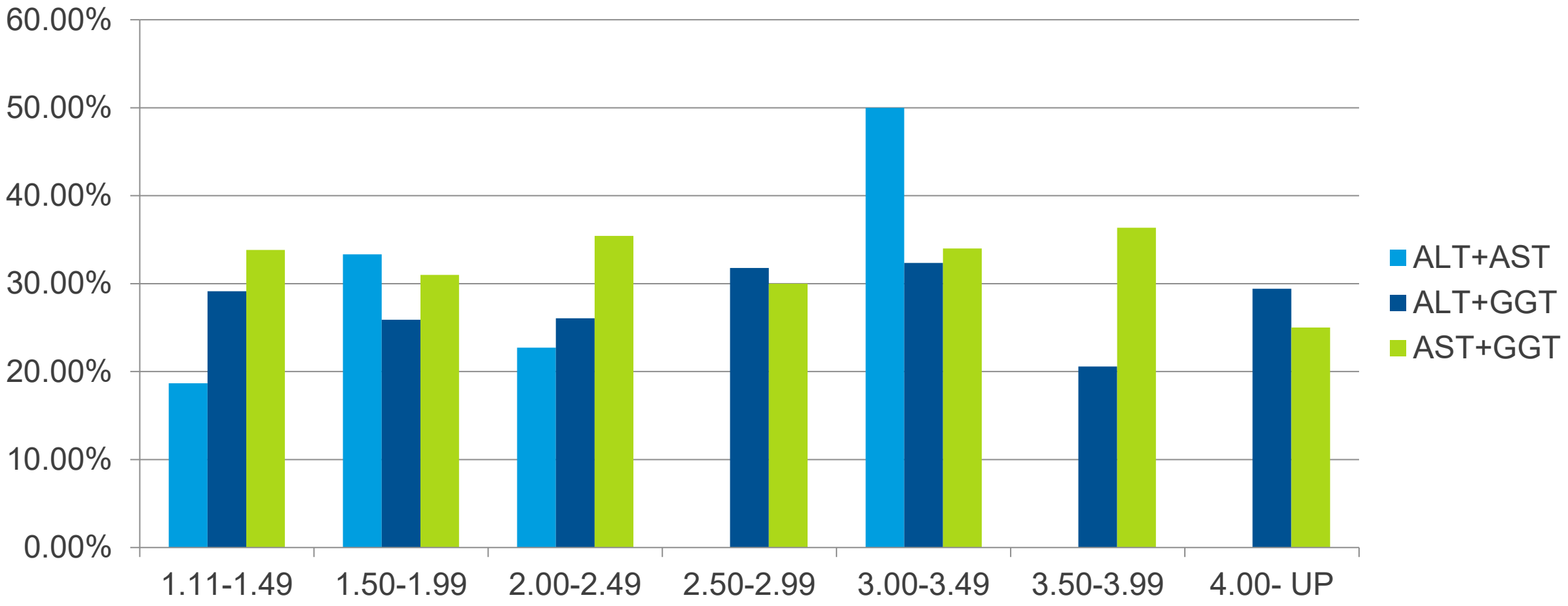
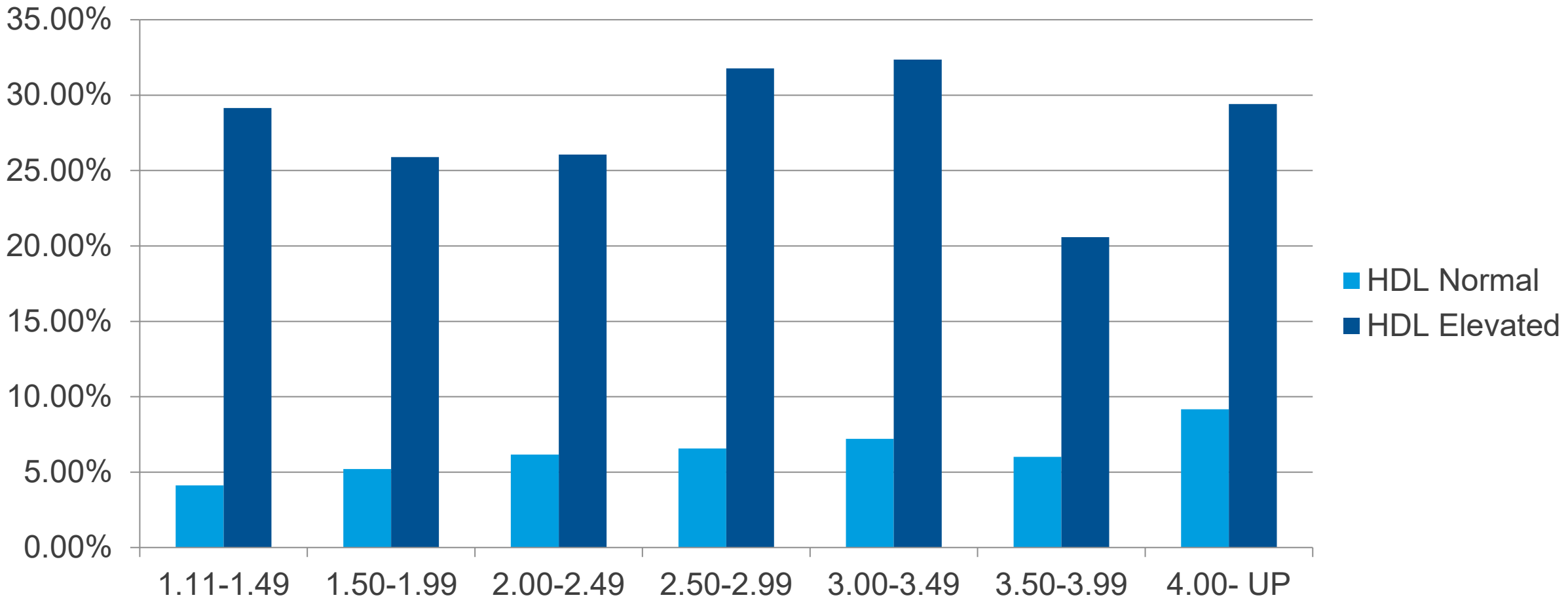
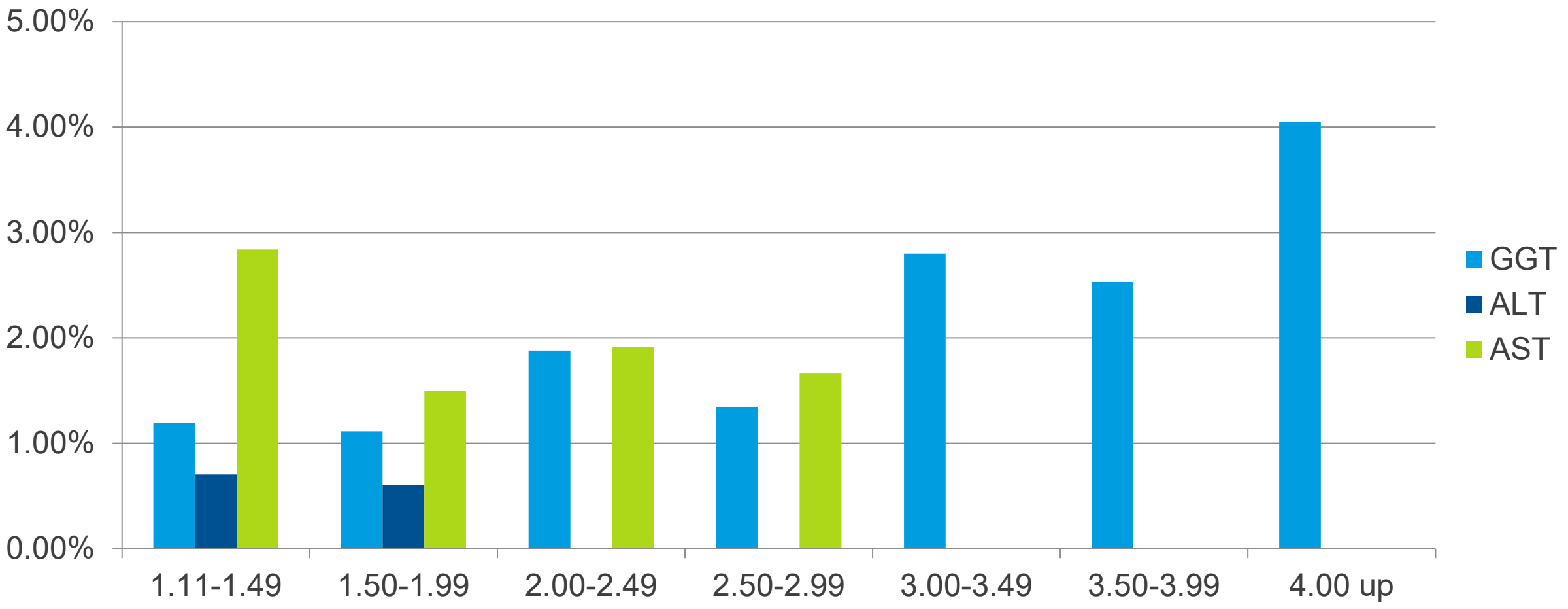
CDT Prevalence by Enzyme – Two Enzymes Elevated
HDL Elevated



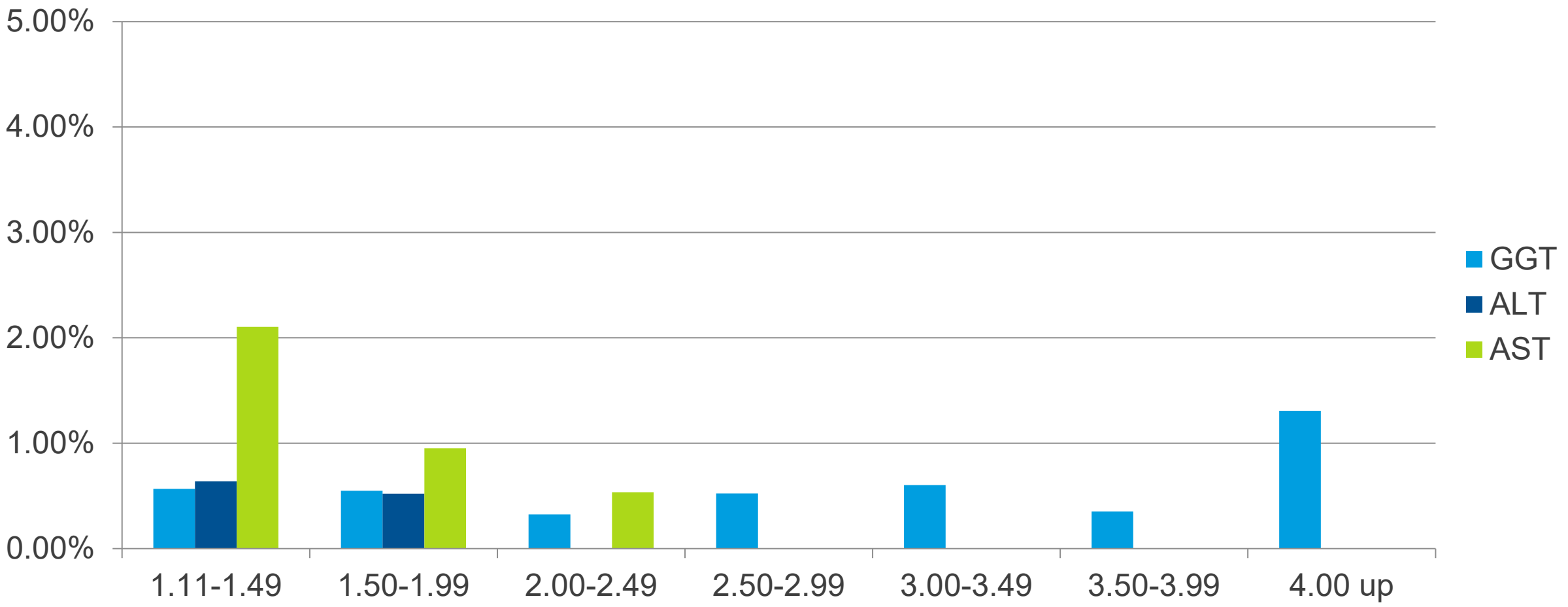
CDT Prevalence by Enzyme All Enzymes Elevated



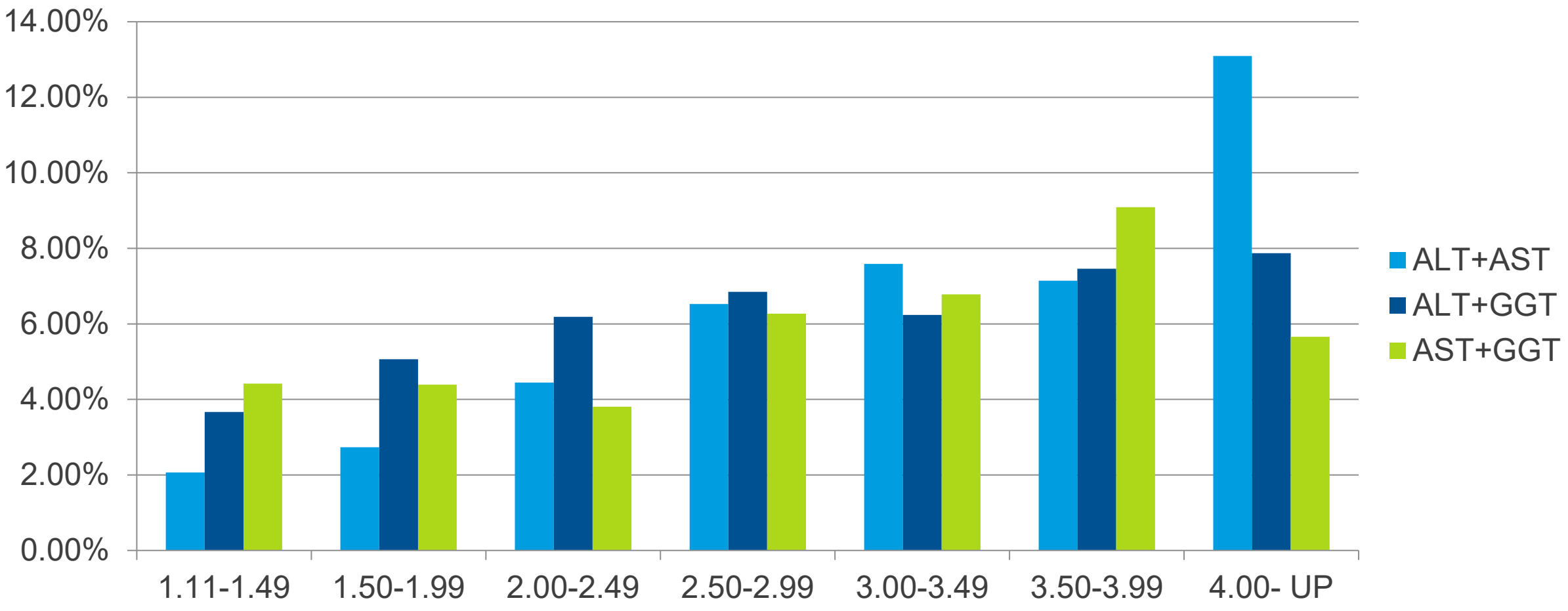
Hepatitis C Antibody – Single Enzyme Elevated



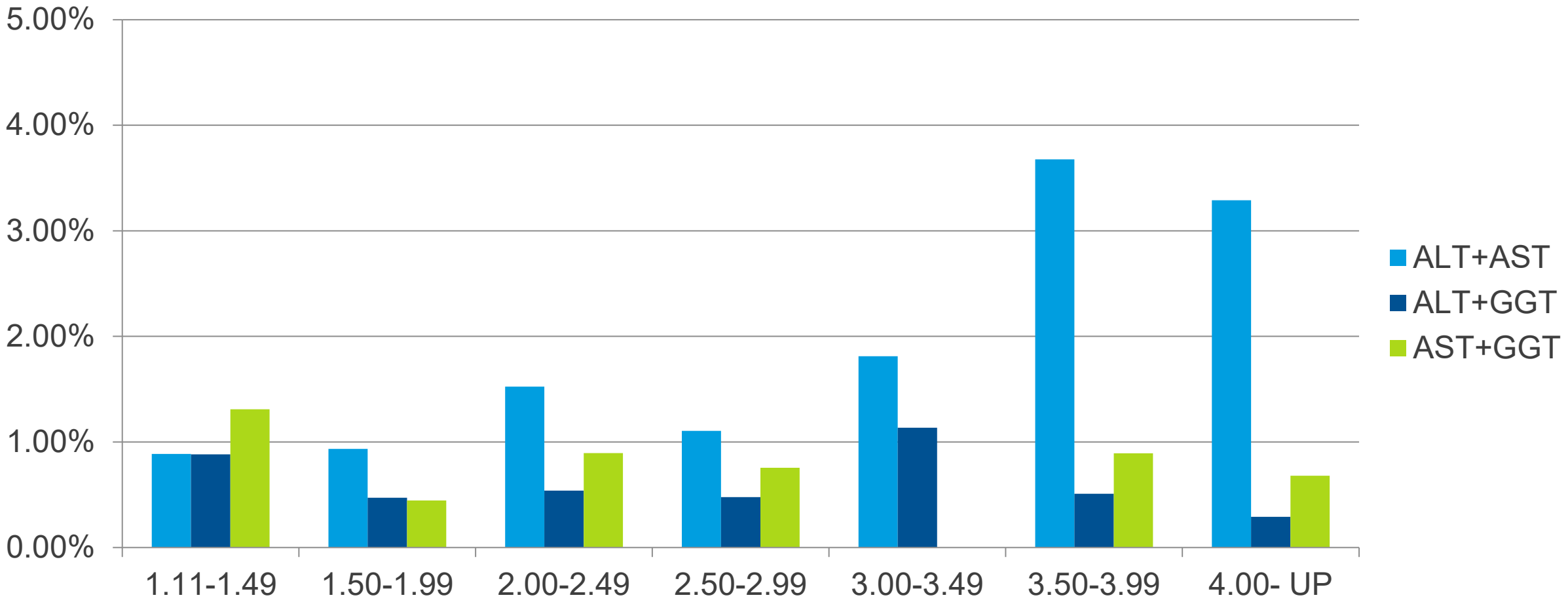
Hepatitis B Antibody – Single Enzyme Elevated



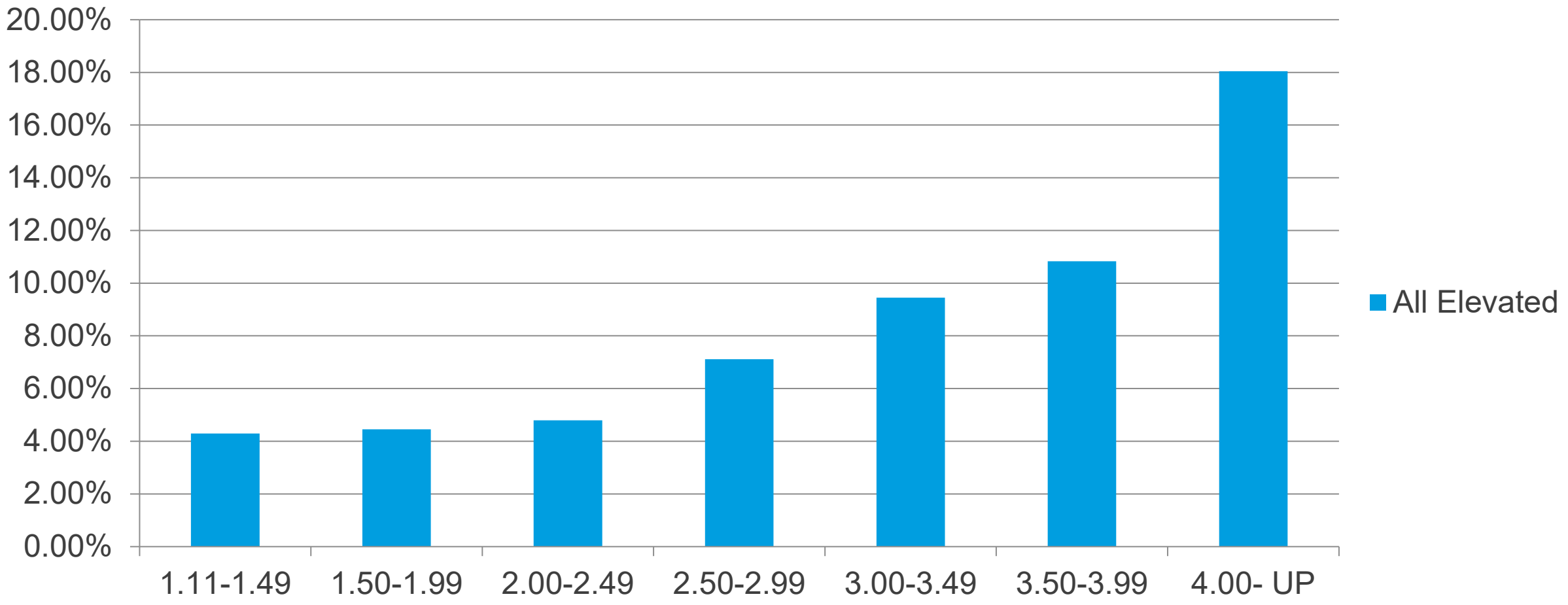
Hepatitis C Prevalence – Two Enzymes Elevated



Hepatitis B Prevalence – Two Enzymes Elevated



Hepatitis C Prevalence by Enzyme – All Enzymes Elevated



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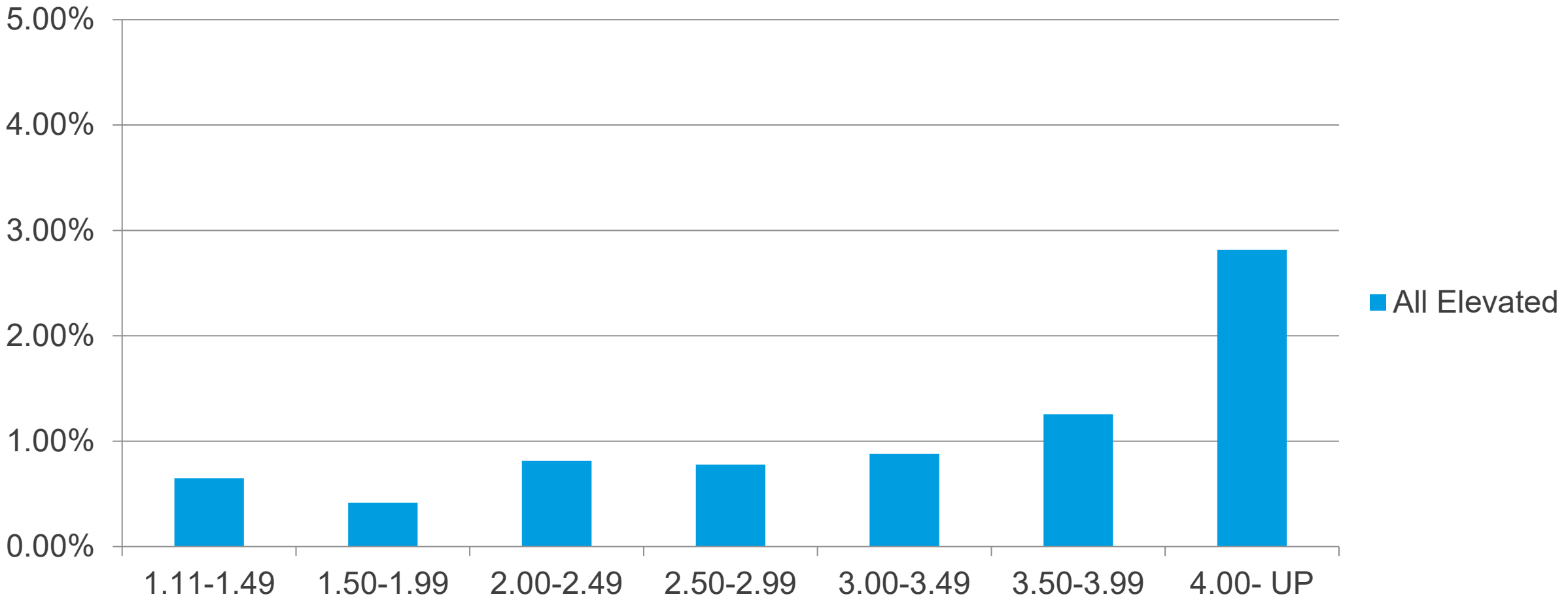
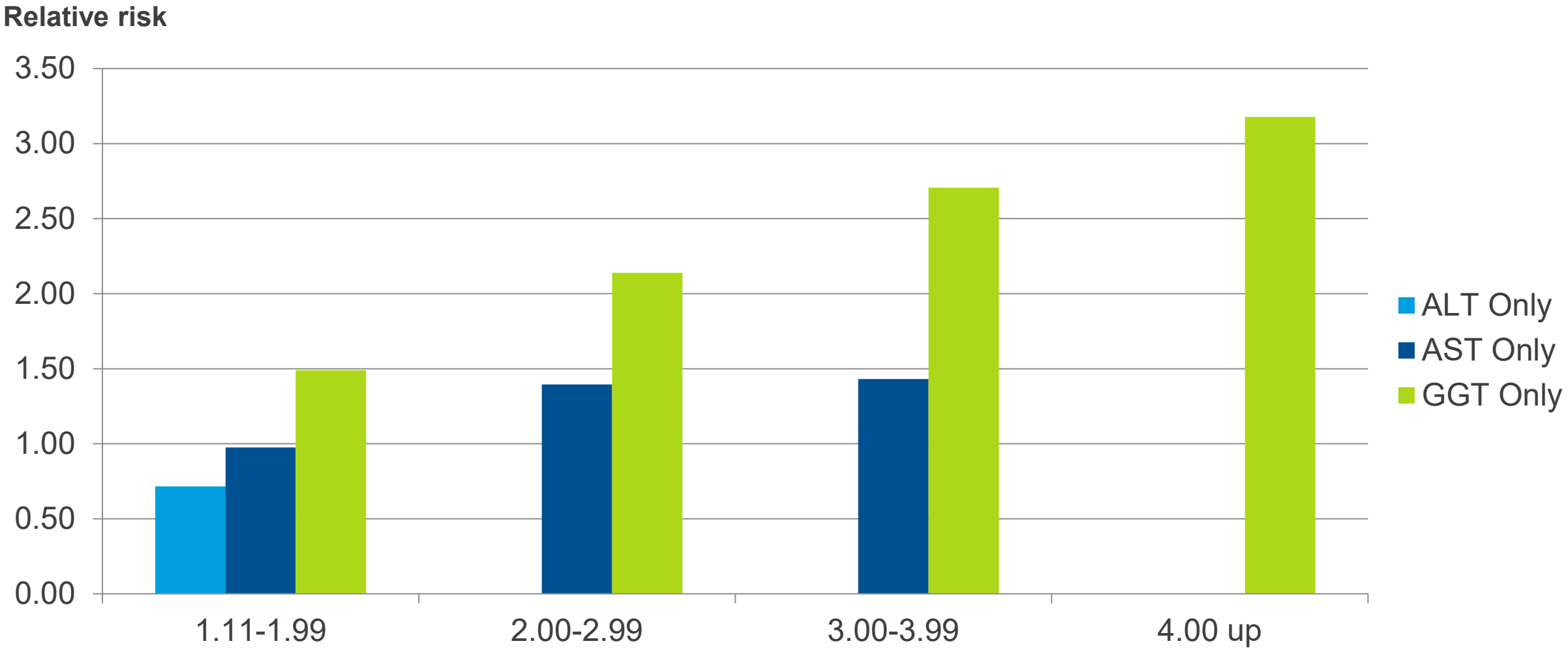
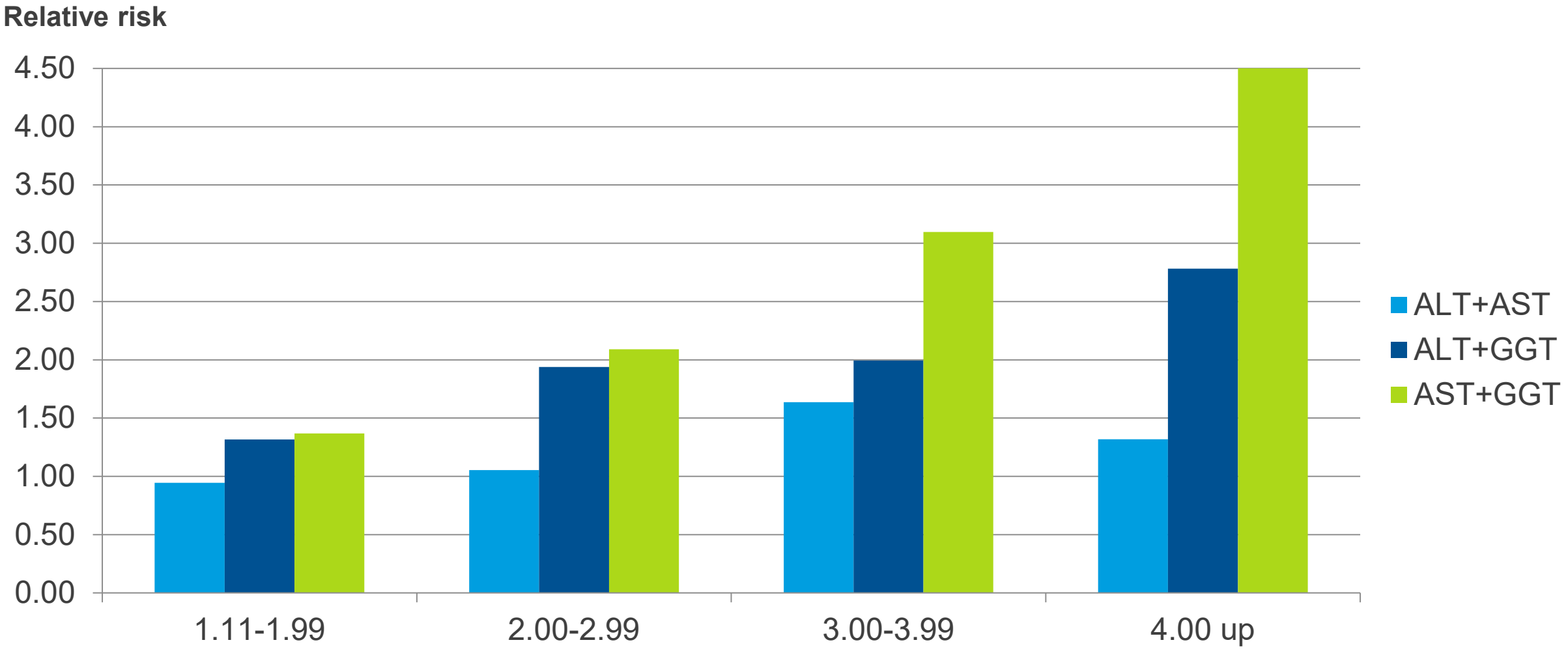
Hepatitis B Prevalence by Enzyme – All Enzymes Elevated



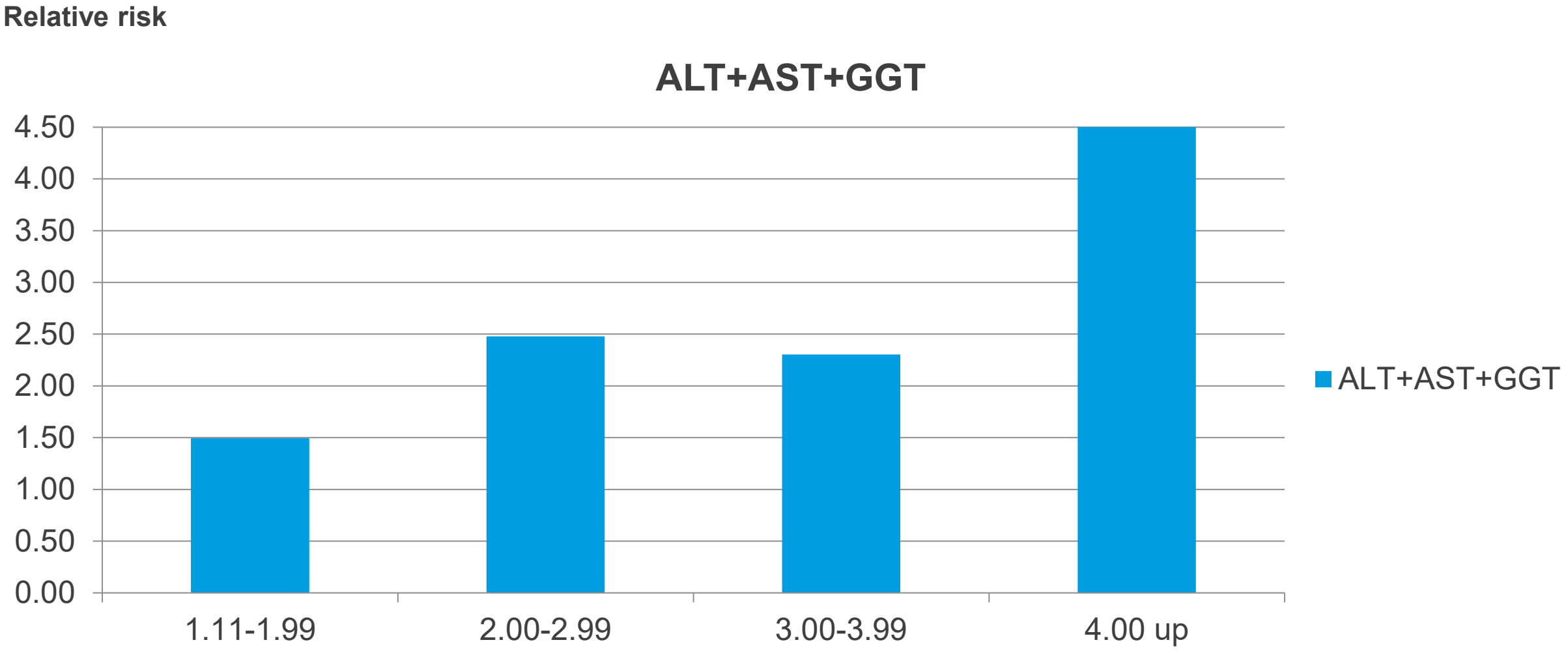
Mortality with a Single Enzyme Only Elevated
Relative risk by degree of elevation and enzyme



Mortality with Two Enzymes Elevated
Relative risk by degree of elevation and enzyme combination

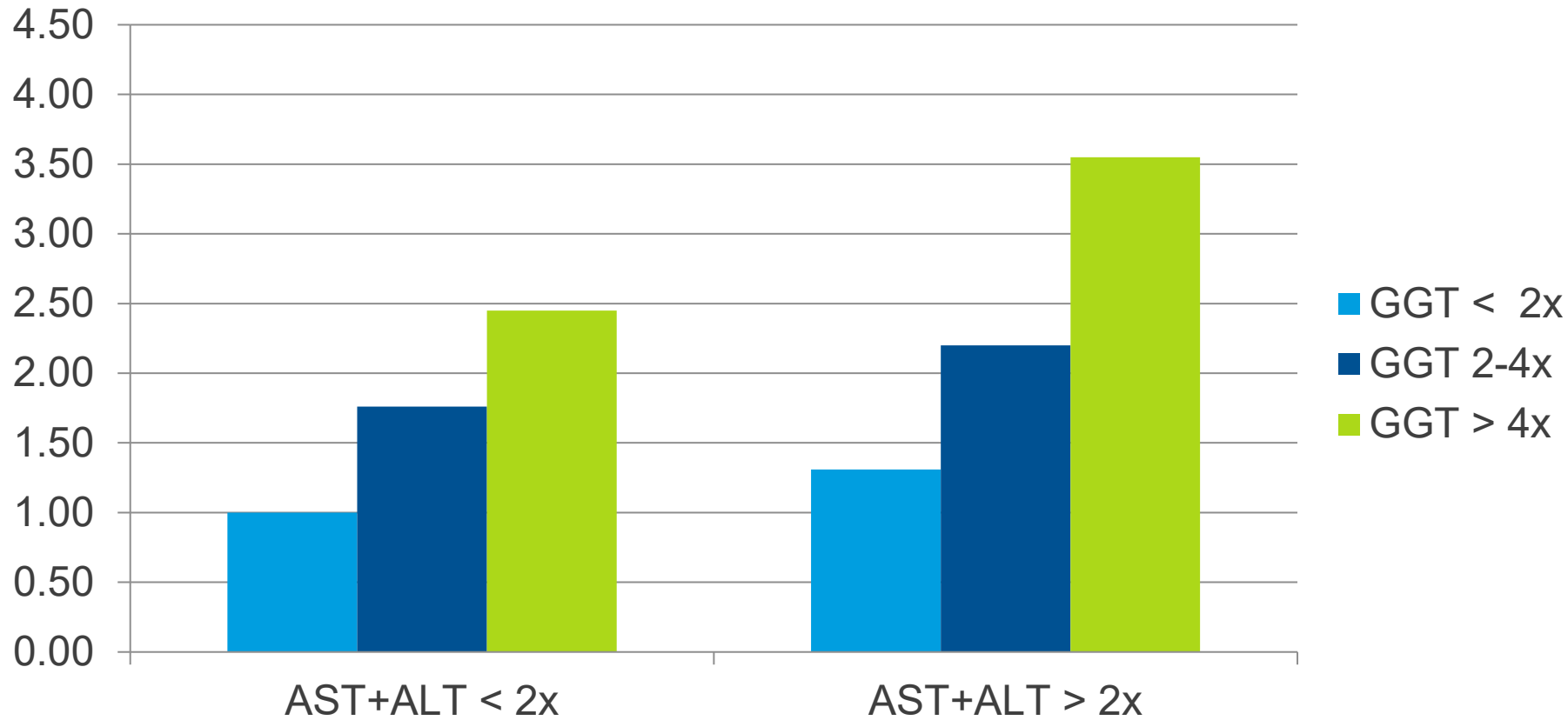


Mortality with Three Enzymes Elevated
Relative risk by degree of elevation and enzyme combination



Mortality in Insured Applicants
Relative risk by degree of elevation and enzyme combination

Risk Ratio



Pinkham CA, Krause KJ J Insur Med, 2009; 41:170-177.

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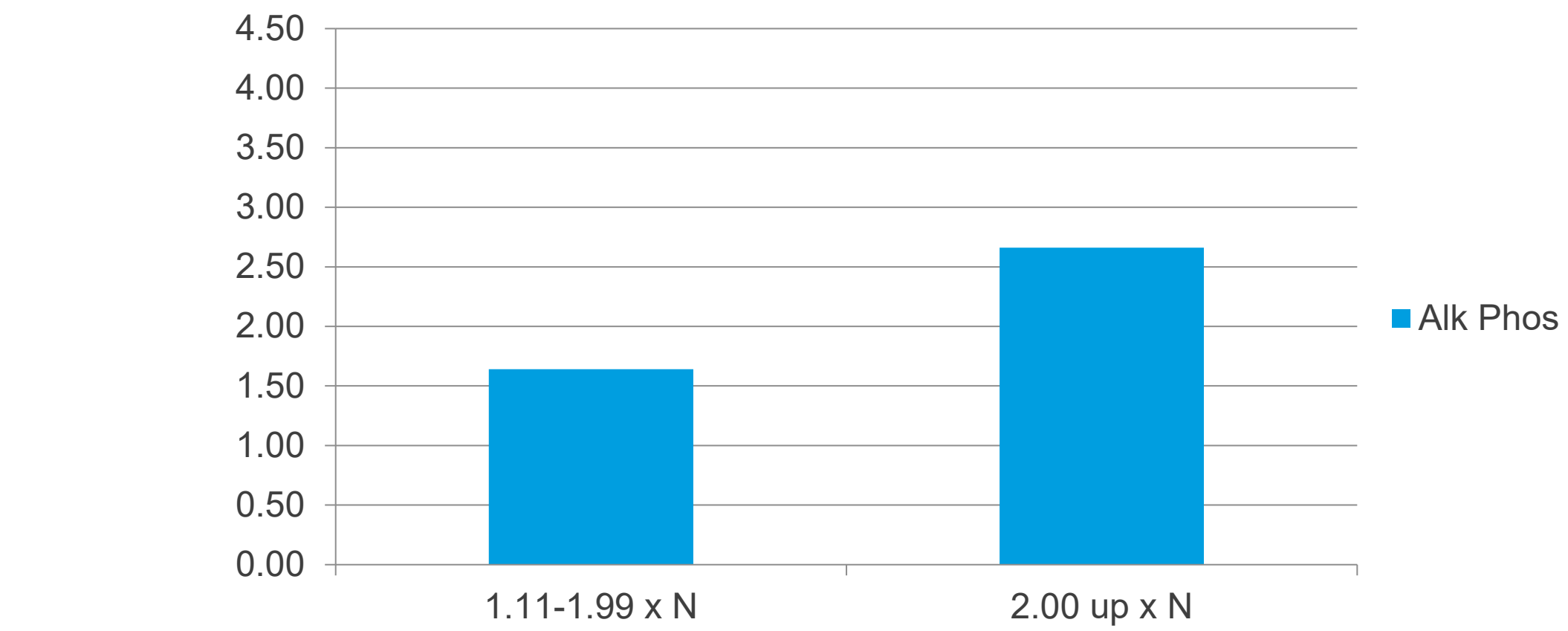
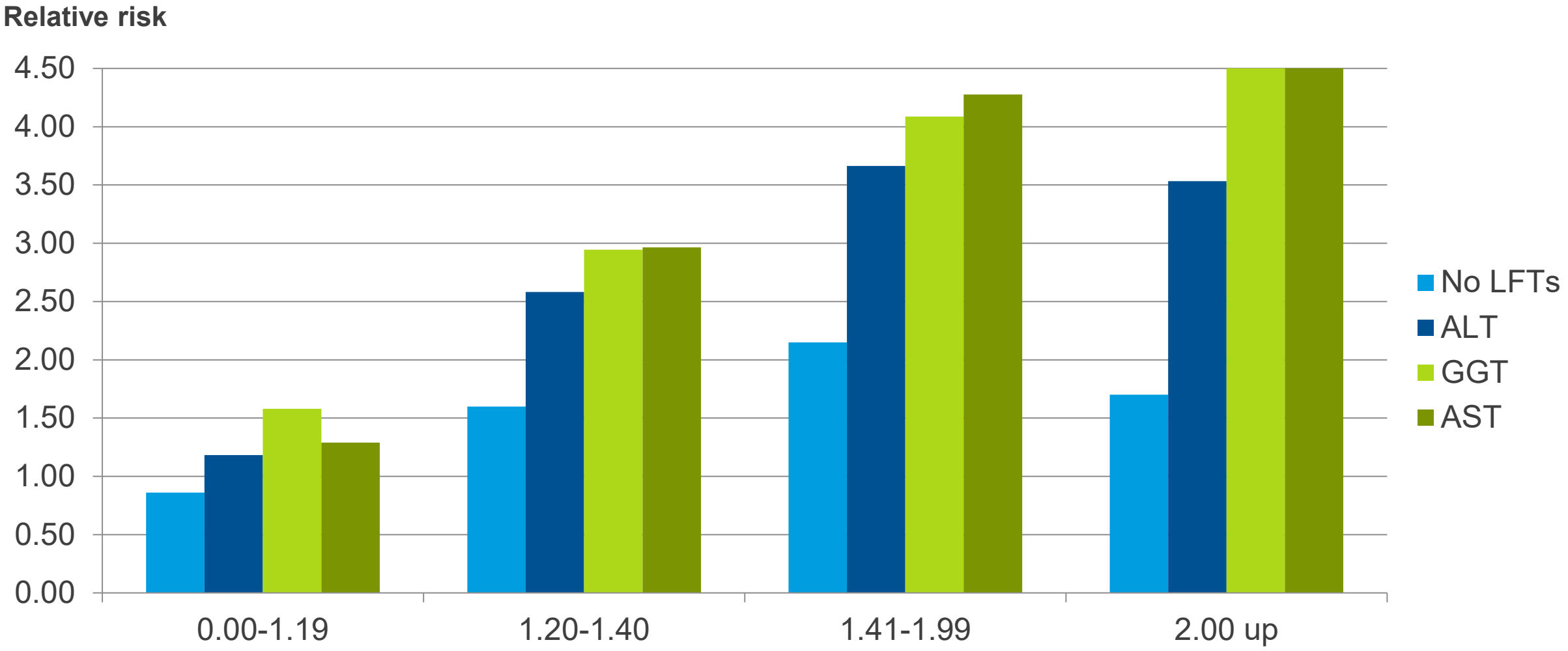
Mortality with Alkaline Phosphatase Elevated
Relative Risk by Degree of Elevation

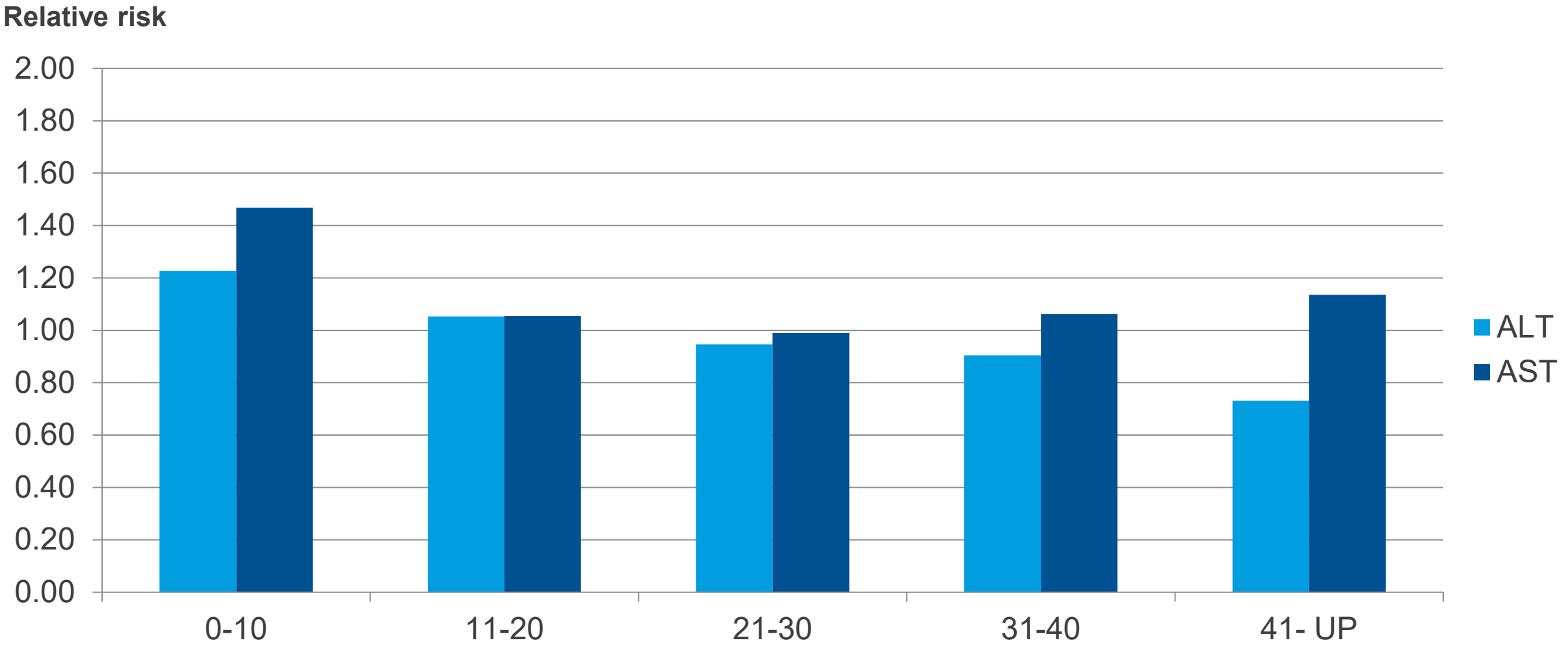


Pinkham CA, Krause KJ J Insur Med, 2009; 41:170-177.

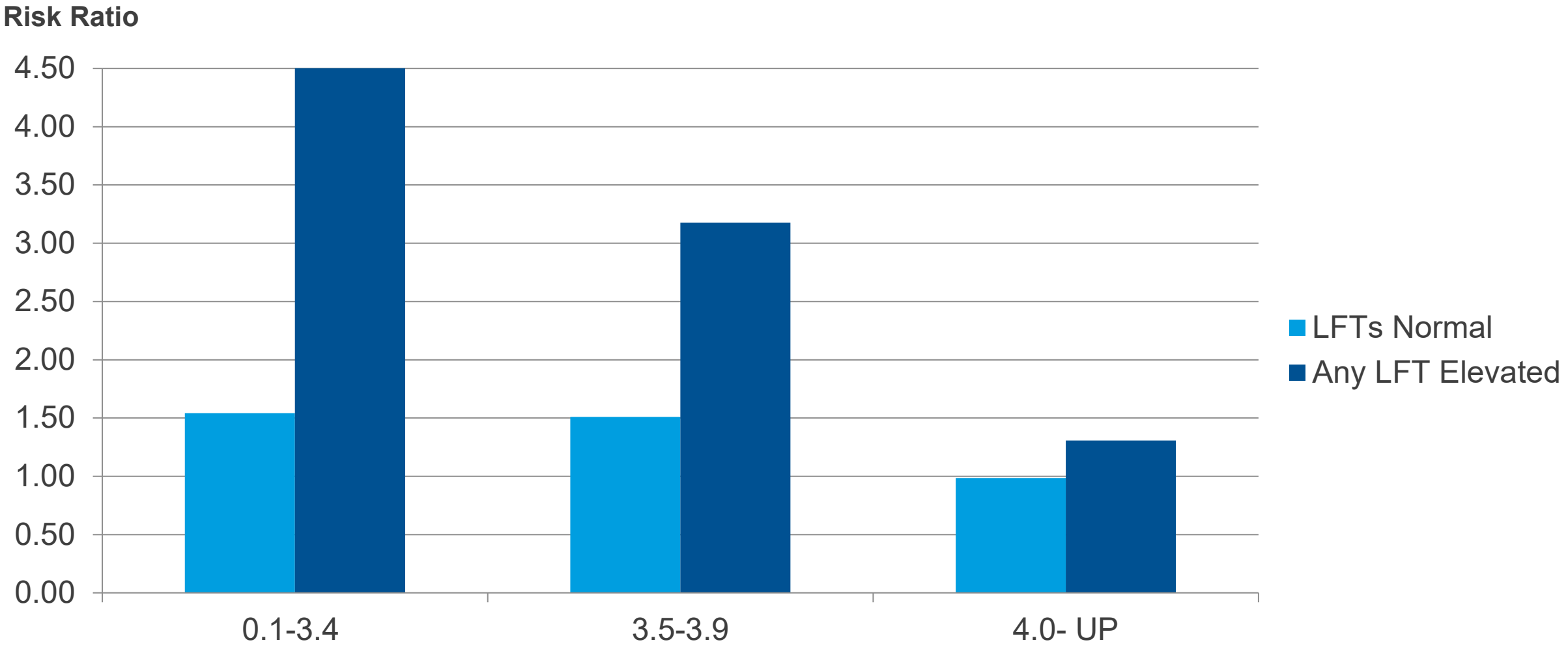
Mortality with Alkaline Phosphatase Elevation
Relative risk by degree of elevation and LFTs



Mortality with Low Values for ALT and AST
Relative risk by absolute values (U/L)



Effect of Low Albumin with and without Elevated LFTs
Relative risk by level of serum albumin (mg/dl) and LFT status



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