



VISUALIZATION OF LIVER TESTS IN SHIFT PLOTS INTEGRATING MULTIPLES OF BASELINE AND UPPER LIMIT OF NORMAL

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Background:

In 1978, Dr. Hy Zimmerman observed that drug induced liver cell injury that resulted in jaundice was associated with a 10-50% risk of death. A Hy's law case (increase in aminotransferase >3x the reference upper limit of normal (ULN), bilirubin >2xULN with no initial cholestasis) in 1000 patients thus could predict severe liver injury at a rate of 1 in 10,000 when alternate sources of liver injury are excluded by expert review¹.

The Evaluation of Drug Induced Serious Hepatotoxicity (eDISH) tool developed by FDA experts helps reviewers visualize possible Hy's law cases and has been widely integrated into clinical review². The use of the tool, along with the expert consultation provided by the Office of Surveillance and Epidemiology, has enabled DILI prediction such that no new drugs have been approved and subsequently withdrawn due to unrecognized DILI risk since 2005. The predictive value of Hy's law for death or transplant within 6 months is higher in patients with chronic liver disease (16% PPV); varying from 15.4% for patients with chronic HCV to 8.3% for patients with nonalcoholic liver disease³. Patients with hepatitis C improve their liver tests with effective treatment.

The hepatotoxicity attributed to a new drug is complicated by use with hepatitis C drugs that could, independently or through interaction, cause hemolysis, rhabdomyolysis, lactic acidosis, mitochondrial toxicity. Review tools that can enable a quick exploration of the shifts in hepatic analytes from their baseline values can be useful in identifying subjects for referral to FDA hepatic experts.

Methods:

We describe the baseline and postbaseline hepatic analytes of patients who received a new drug for hepatitis C and present a data visualization that integrate the eDISH plot findings (both baseline and postbaseline quadrant locations based on the ULN for bilirubin and Alanine aminotransferase) in a shift plot of the same analytes over their baseline values.

Results:

The values for the ULN in this study varied by as much as 10 units for ALT and 30 units for ALP. Baseline values for ALT, AST and BILI/ALP were within the ULN for 22%, 29%, 96%, respectively. Postbaseline peak maximum values were 10-fold the baseline maximum for ALT, 20-fold for AST, 5-fold BILI.

The integrated plots enabled visualization of the change from BLN for individuals and the entire study population

- The majority of subjects experienced postbaseline decrease in ALT compared to their baselines. The decrease in ALT is consistent with the conclusion that treatment was effective in treating hepatitis C (decreased viral load, data not shown).
- However, the majority of subjects had postbaseline increase in BILI compared to their baselines. The drug is administered as part of a regimen in combination with ribavirin which induces hemolysis and could account for the increase in BILI. A minority of patients showed a reduction in both ALT and BILI from their baselines.
- Of 18 possible Hy's law cases identified through eDISH, 9 patients developed >3x increase in both ALT and BILI from their baselines. Six of the remaining 9 had more extreme BILI elevations compared to ALT.
- Among patients in the Temple's corollary, 5 had postbaseline ALT more than 5xBLN. Particularly, one patient had postbaseline ALT > 36x and BILI > 3x of its baseline values.
- Using eDISH plot, a patient in Hy's law quadrant on treatment would have been classified in Temple's corollary at baseline. However, its ALT declined below baseline value on treatment.

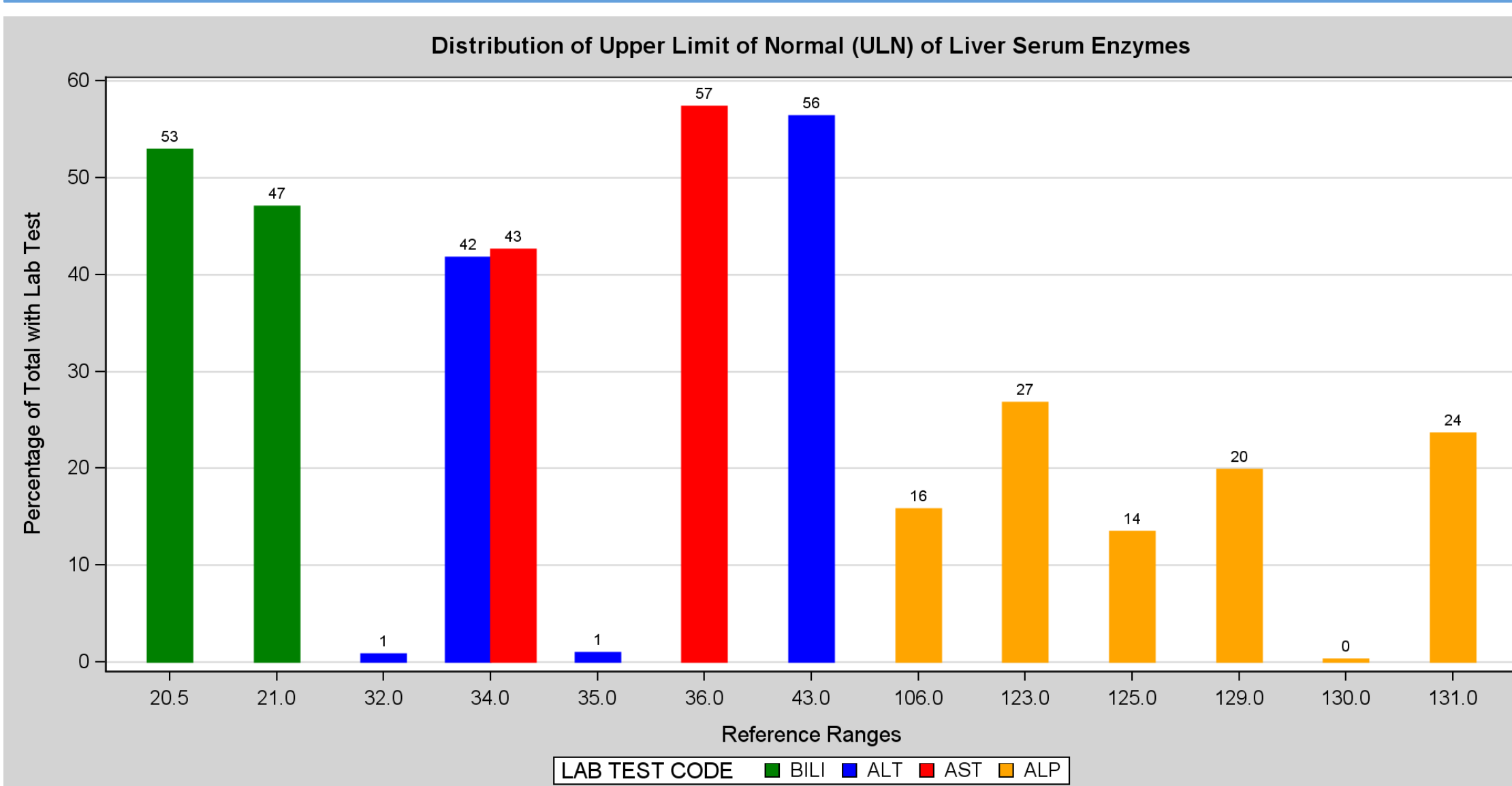
Conclusion:

The variability in ULN reference ranges can influence the DILI evaluation in the eDISH plot. To take this variability into account, outlier analyses could be helpful in assessing liver adverse events. This composite visualization of eDISH and shifts from baseline can be helpful in assessing such events and can describe the changes in both ALT and BILI for individual patients and for the treated population. This in turn, could prompt consultation with the liver experts at FDA, and facilitate the review of liver test data in patients with liver diseases.

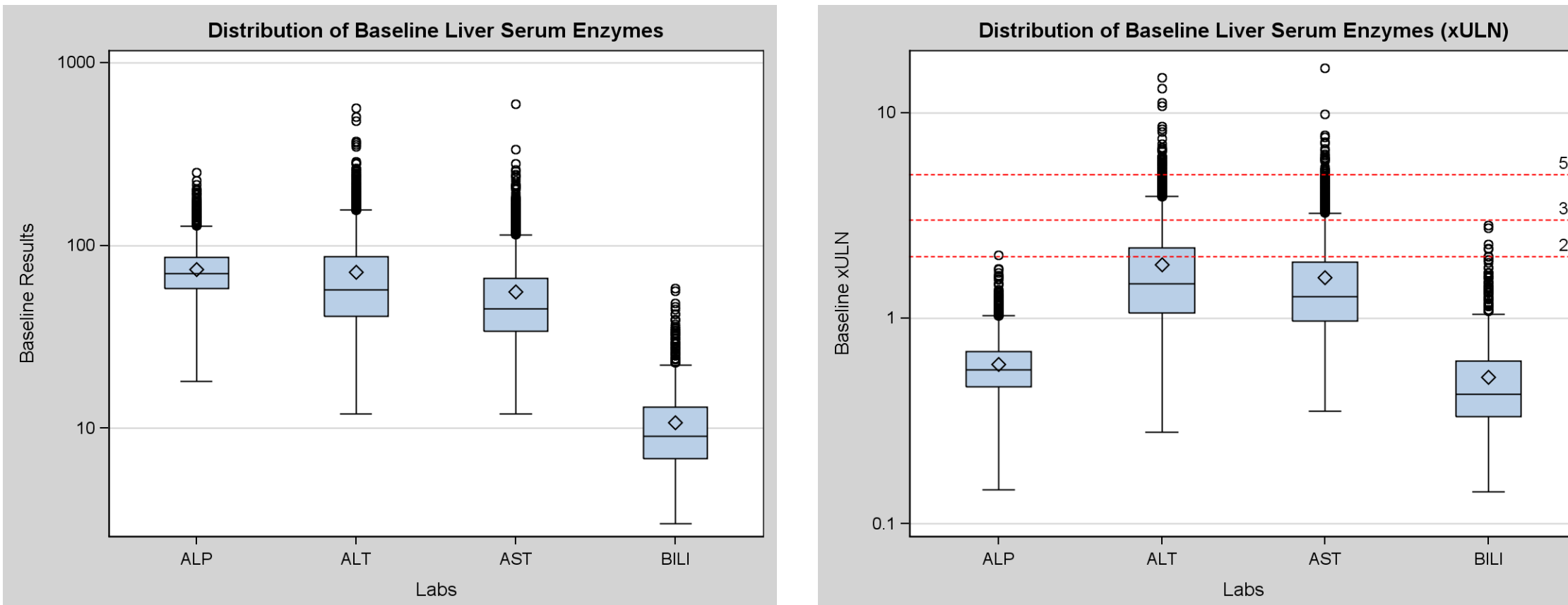
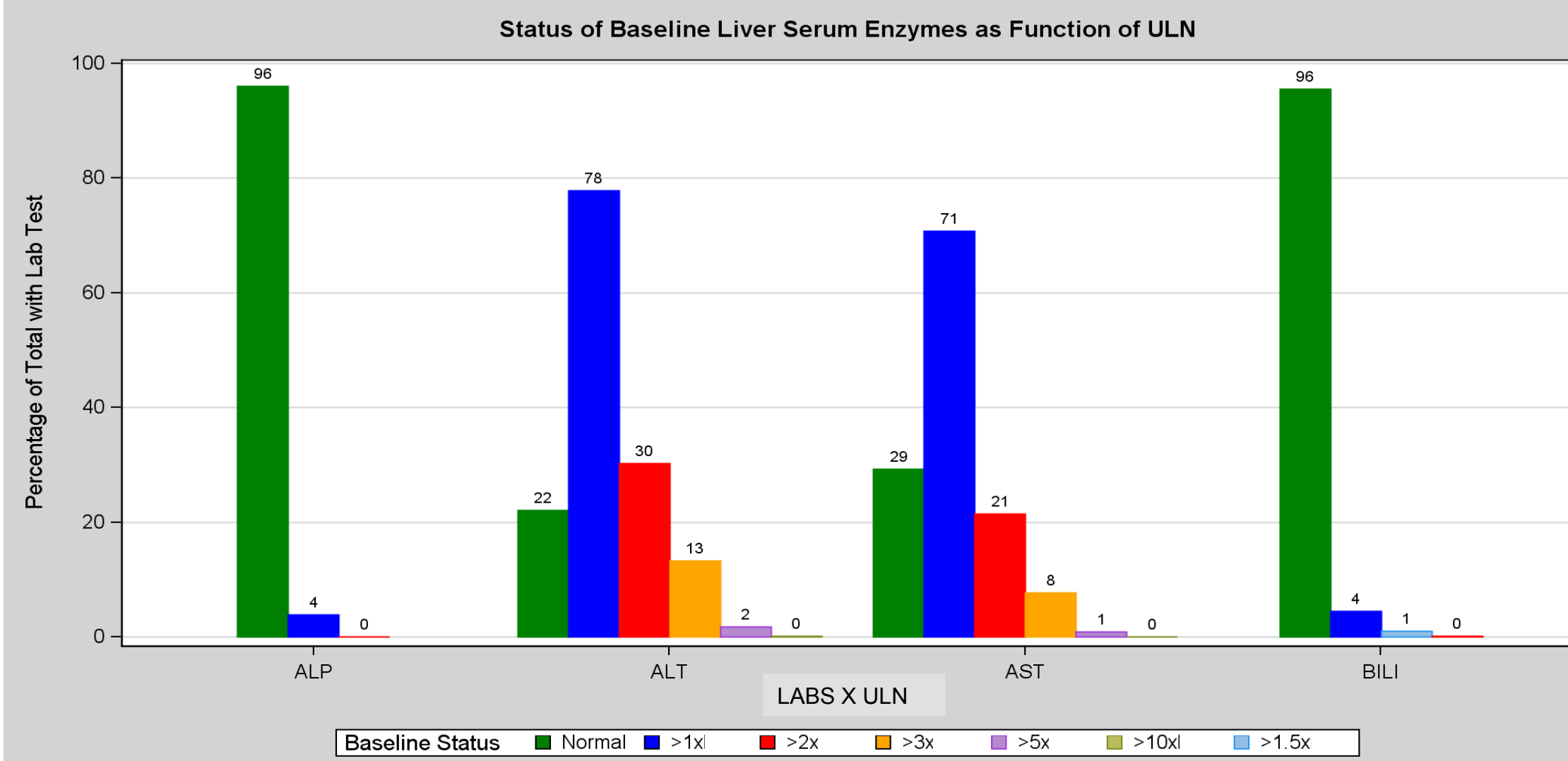
References:

- Guidance for Industry Drug-Induced Liver Injury: Premarket Clinical evaluation-2009
- Ted Guo, John Senior, Kate Gelperin. How a SAS/IntrNet tool was created at the FDA for the detection of potential drug induced liver injury using data with CDISC standard at <http://www.lexjansen.com/wuss/2009/cdi/CDI-Guo.pdf>
- Paul Hayashi. Hy's Law and Pre-existing Liver Disease at <http://www.aasld.org/sites/default/files/documents/DILI/2015/S4P2-Hayashi.pdf>

BASELINE LIVER TEST RESULTS



This chart shows the ULN reference values used in each test and their respective frequencies in percentiles. The reference range was most variable for alkaline phosphatase.



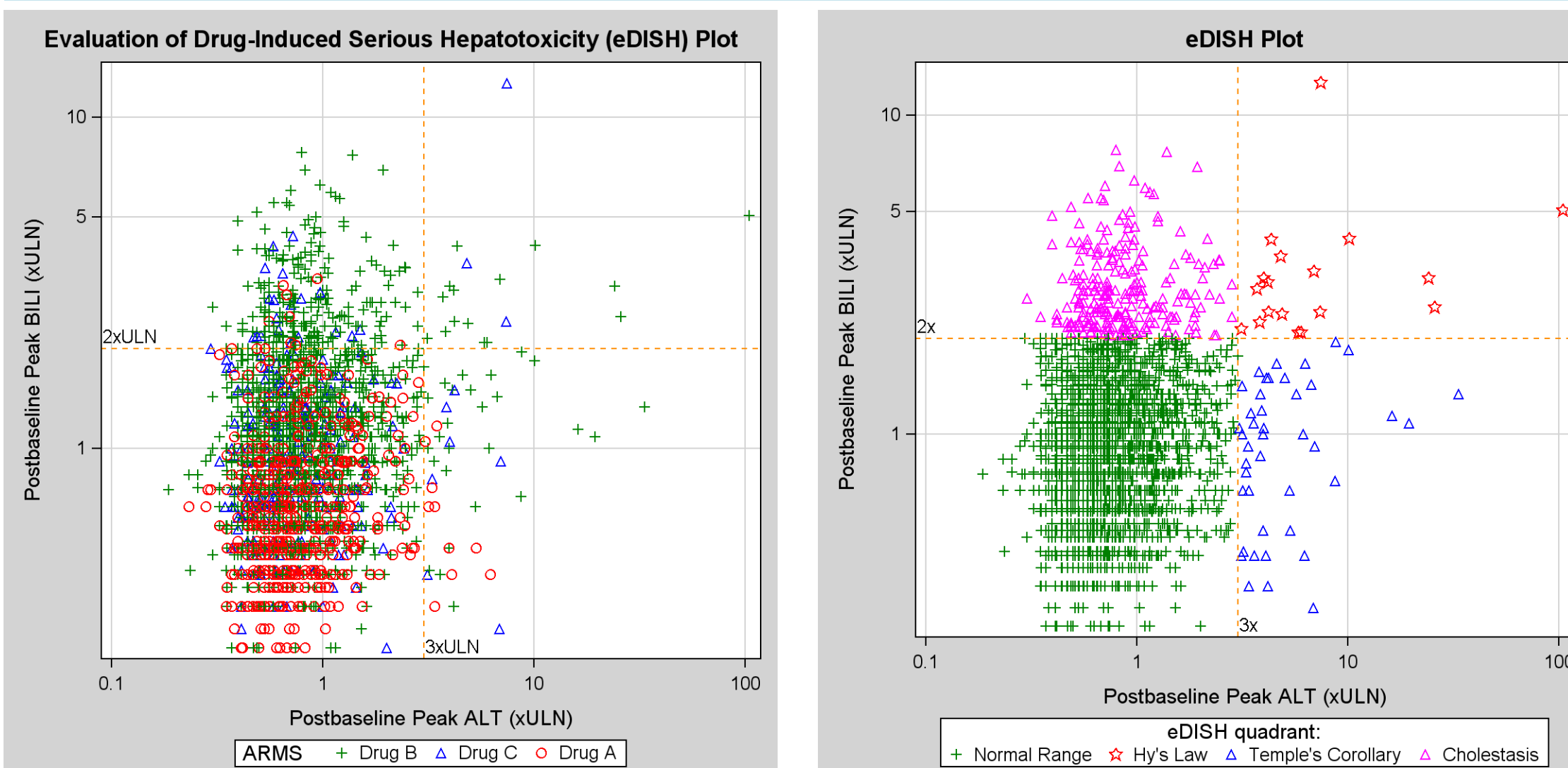
The baseline liver test results in mostly non-cirrhotic patients in this trial show

- the distribution of each test was skewed to the right with several outliers
- there was a greater variability in the aminotransferases
- for ALT and AST, the 3rd quartile was around 2xULN and the 1st quartile was around 1xULN
- 4.5% of the population had increased total bilirubin above the ULN

BASELINE & ON-TREATMENT LIVER TEST RESULTS

	ALP	ALT	AST	BILI
N	2628	2628	2628	2628
Baseline Value				
Mean ± SD	73.95 ± 24.67	71.37 ± 47.04	55.62 ± 34.37	10.68 ± 5.5
Range (min - max)	18 - 250	12 - 564	12 - 595	3 - 58.15
Median(Q1 - Q3)	70(58 - 86)	57(41 - 87)	45(34 - 66)	9(6.84 - 13)
Postbaseline Peak Value				
Mean ± SD	88.46 ± 29.96	39.87 ± 102.44	36.91 ± 238.57	23.41 ± 17.36
Range (min - max)	20 - 442	8 - 4682	11 - 12174.5	5.13 - 259.12
Median(Q1 - Q3)	84(68 - 102)	28(21 - 41)	26(22 - 34)	18.81(13 - 28)

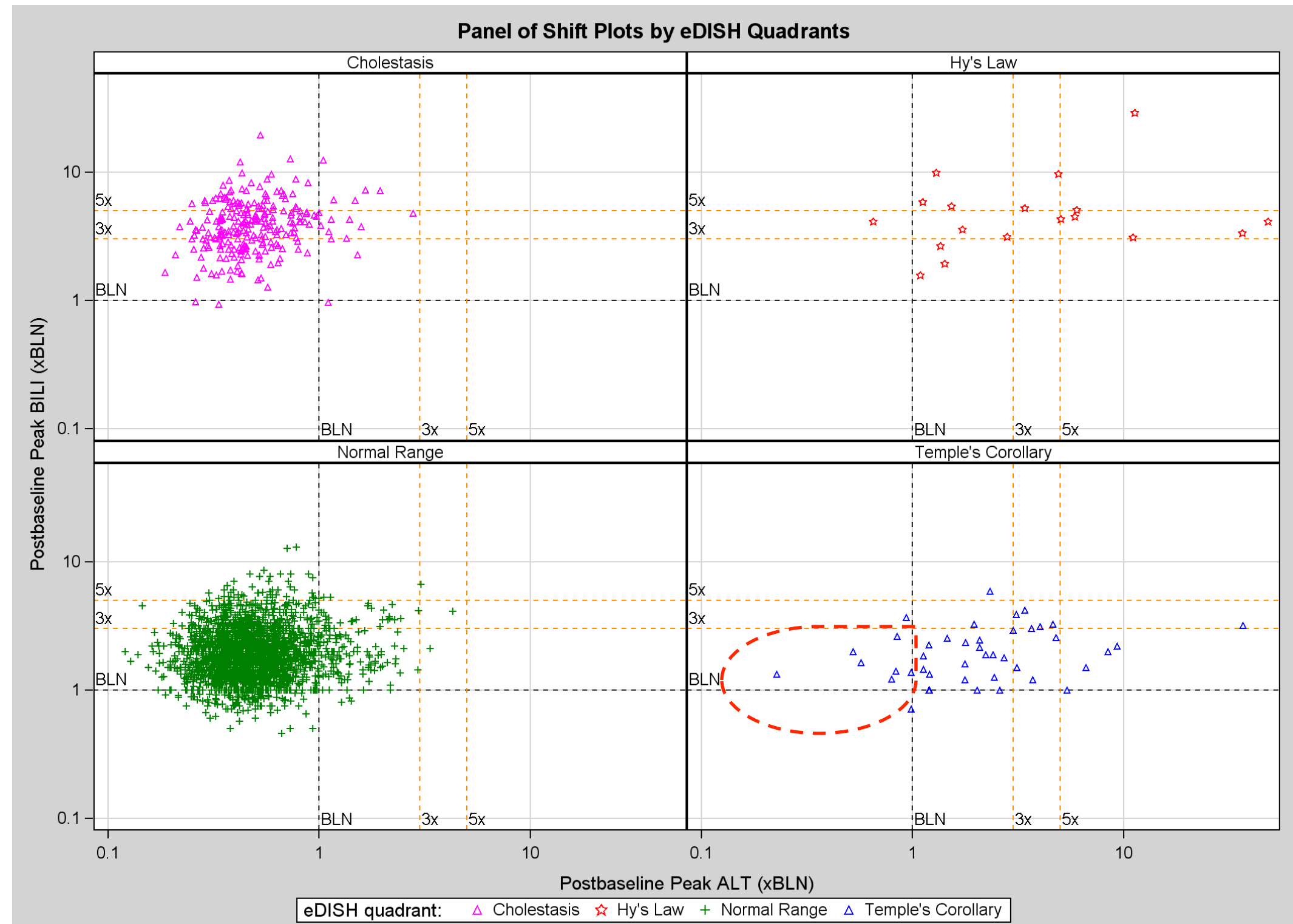
This table provides the statistical summaries of the baseline and peak postbaseline lab test results for each liver serum enzyme.



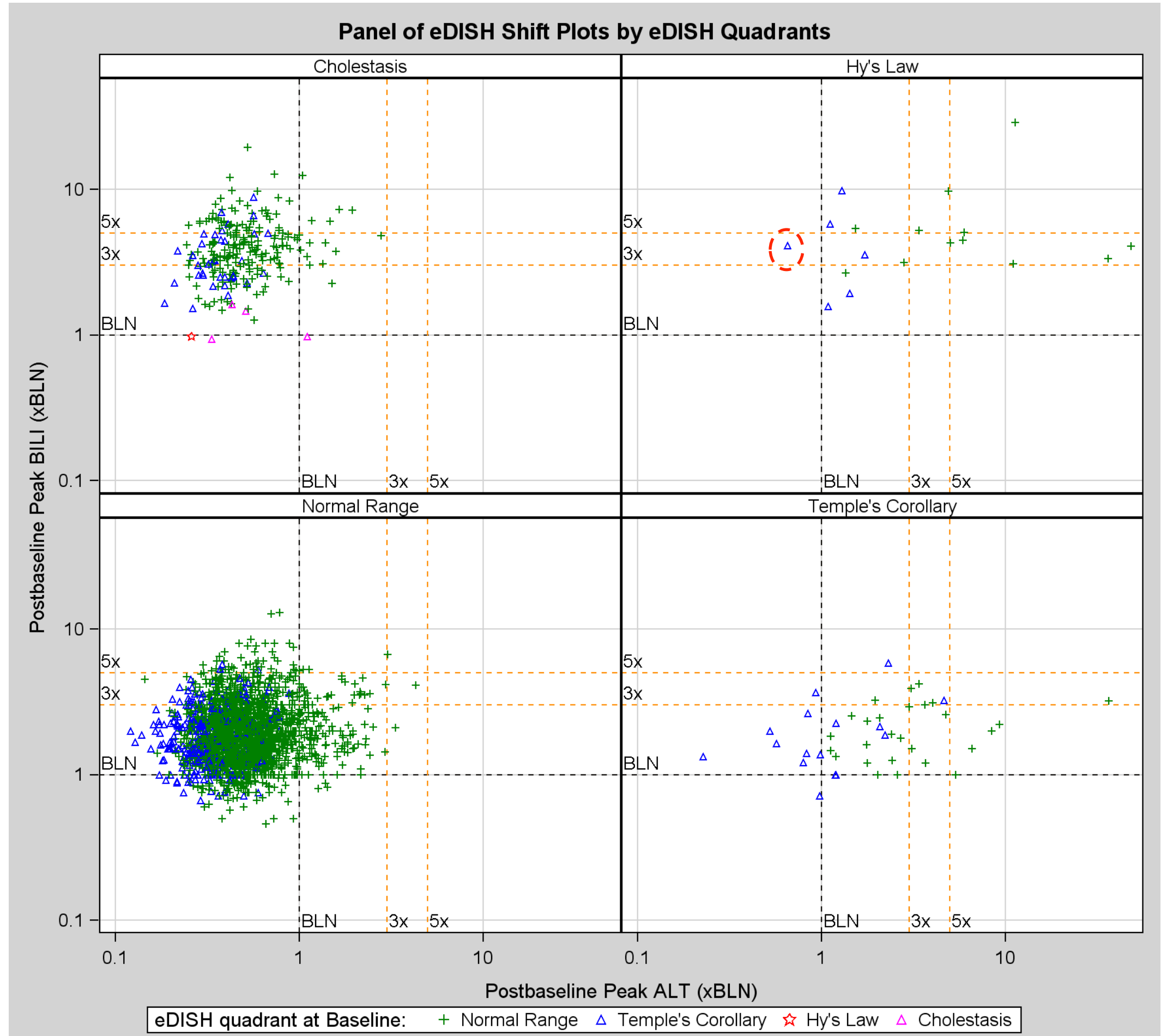
This is the classic eDISH plot which is a log-log scatter plot where the x-axis is the peak postbaseline alanine aminotransferase (xULN) and the y-axis is the peak postbaseline total bilirubin (xULN), with individual patients represented by study treatment arm on the left, and by eDISH quadrant on the right. There were 18 subjects in the Hy's law quadrant, 43 subjects in the Temple's corollary quadrant, and 244 subjects in the Cholestasis quadrant.



In this plot, patients are segregated into 4 panels, corresponding to the quadrant they belong in the eDISH plot. The colored symbols represent each subject as they fall in the eDISH quadrant. However, the data presented in the panel corresponds to each subjects' baseline value as a multiple of the ULN. Thus the shift from baseline to peak postbaseline is represented. For instance, one patient fulfilled Hy's law at baseline and reverted to Cholestasis on treatment. Close to quarter of the patients had ALT >3xULN at baseline that normalized on treatment.

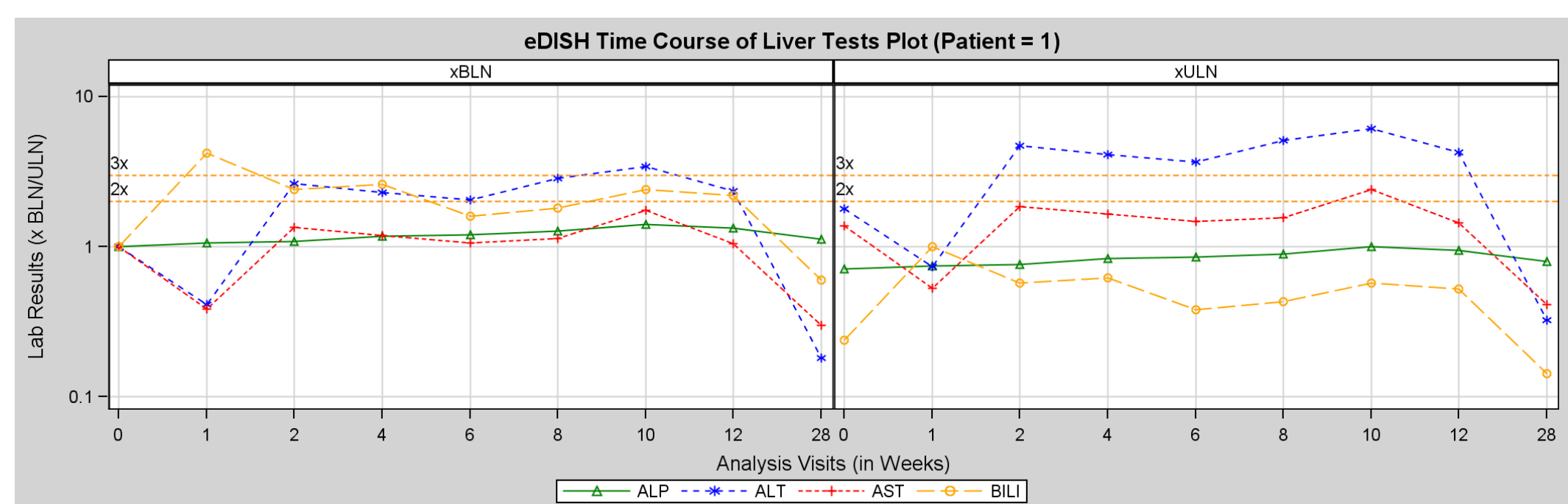


Similarly, this plot represents patients in 4 panels, color coded to correspond to the quadrant they belong in the eDISH plot. However, the data is presented as multiples of the baseline value (BLN) rather than the ULN. The shift in peak postbaseline lab is compared to each patients' baseline value. Several patients in the Hy's law quadrant had ALT closer to their baselines, including one subject with a peak on treatment value lower than baseline, as did several patients in the Temple's corollary. Although most patients had a decline in peak ALT, peak BILI on treatment was > BLN in most patients.

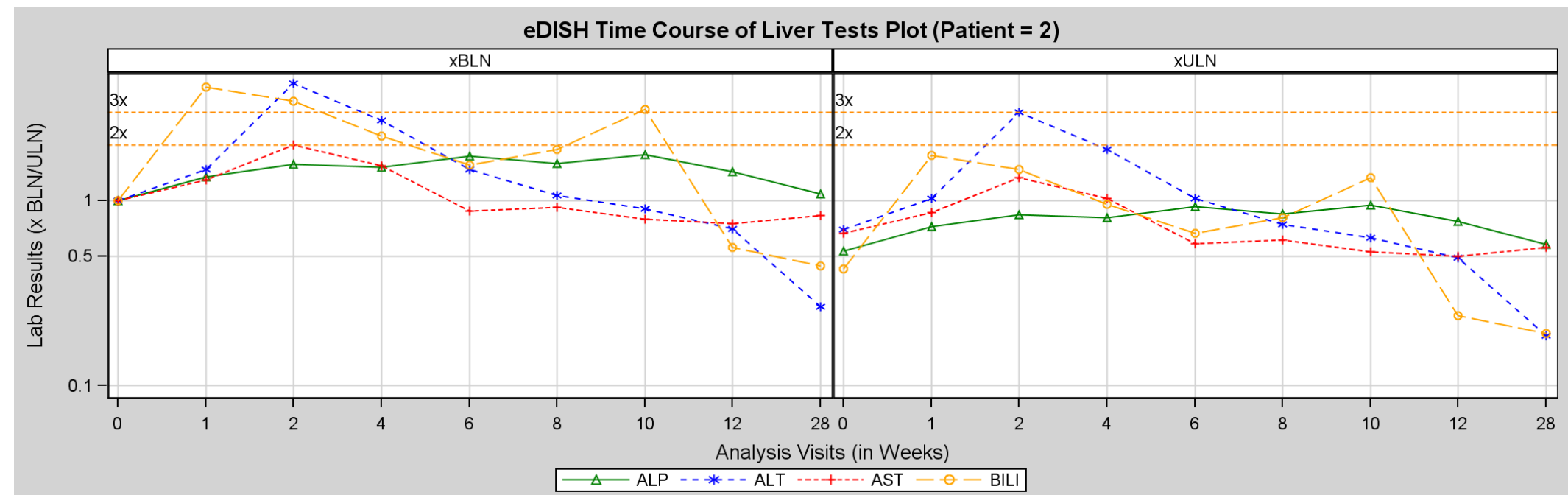


This is a shift plot from baseline to peak postbaseline which integrates the prior two plots. The panels represent the on-treatment eDISH quadrants whereas the colored symbols represent the eDISH quadrants of the BASELINE values (not POSTBASELINE) as multiples of ULN. Note one patient belonging to Hy's law quadrant on-treatment was on Temple's corollary at baseline. But, this patient actually had ALT declined to below its baseline while on-treatment although it still met the 3xULN criteria. Several patients belonging to either the normal range or Temple's corollary on-treatment which were in the normal range at baseline had their BILI and ALT went up to 3-fold of their baselines. Expert evaluation might be considered for these subjects as well. For the number patients, their time course of liver tests are given below.

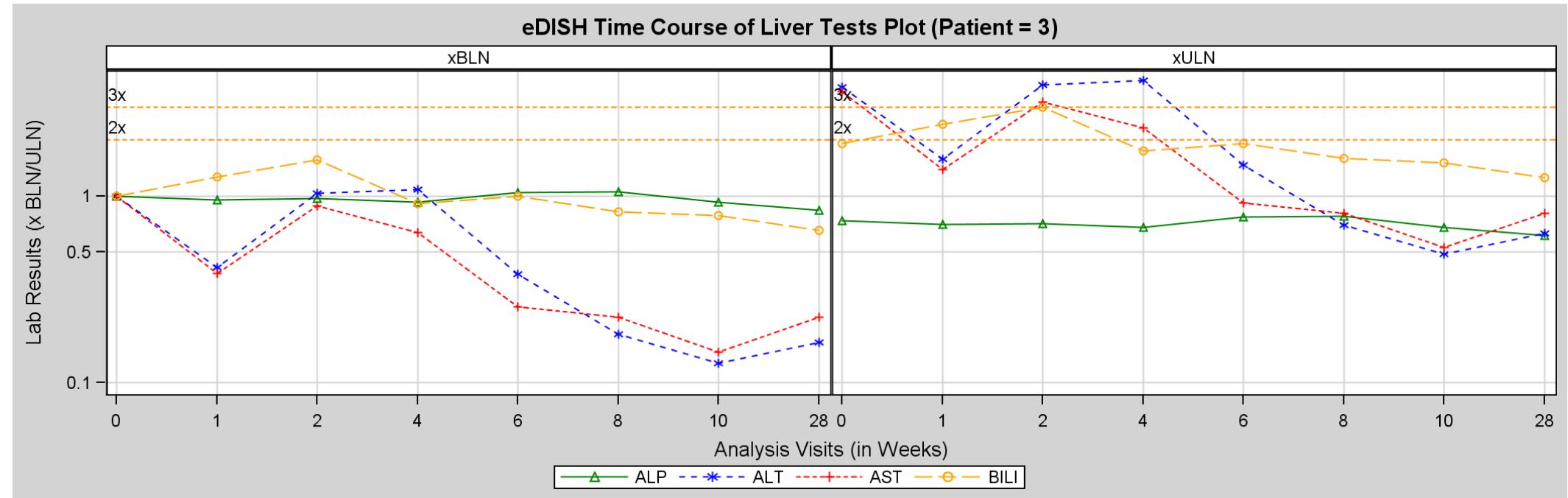
TIME COURSE OF LIVER TESTS AS xBLN & xULN



This case illustrates a patient that had elevated ALT and normal BILI in reference to the established value for ULN and was therefore in the Temple's corollary in the standard eDISH plot. However, this patient also experienced a doubling of its BILI over its baseline, which, taken together with an elevation of ALT over BLN and ULN, could warrant further scrutiny for DILI.



This patient's ALT and BILI values rose on-treatment to over 3x the baseline values although the peaks remained within the normal range in terms of the ULN. Hence, this patient may also warrant further scrutiny for DILI.



This patient seemed to benefit from treatment as demonstrated by sharp decline from its baseline ALT and almost stable BILI in terms of BLN. Moreover, its peak ALT on treatment was not significantly different from its baseline value. Hence, despite identification in the eDISH plot as a possible Hy's law case, this patient might not be as concerning as a potential DILI case.

Abbreviations:

- ALP = Alkaline phosphatase (IU/L)
- ALT = Alanine aminotransferase (IU/L)
- AST = Aspartate aminotransferase (IU/L)
- BILI = Total bilirubin (umol/L)
- BLN = Baseline value
- DILI = Drug induced liver injury
- eDISH = Evaluation of Drug Induced Serious Hepatotoxicity
- Q1 = First quartile
- Q3 = Third quartile
- SD = Standard deviation
- ULN = Upper limit of normal reference