Dear Editor,

We appreciate the time and effort expended by the Reviewers in their evaluation of our manuscript. We do not wish to appear ungrateful or unduly critical but, in truth, some of the criticisms are difficult to understand fully because the English used by the Reviewers has serious grammatical errors. We will therefore try to paraphrase the criticisms as best we can and hope that we capture the meaning that the Reviewers intended. We appreciate that the Reviewers, who are experts in their fields, are not native English speakers and do not appear to have a good written command of the language. The only point to be made is that our ability to address the critique depends on it being comprehensible expressed. We do not wish to appear rude or derogatory.

We have tried to incorporate the responses to the criticisms into the revised manuscript.

First Peer review: This Reviewer considers that the manuscript is valuable but takes issue with the use of the term "Biliary Colic" that he/she feels should be used for both the pain of gallbladder colic (which is classically attributed to contraction of the cystic duct around a luminal stone) and the pain that comes from the passage of a gallstone/gallstones along the common bile duct. This is distinct from the pain of gallbladder inflammation i.e. cholecystitis. The definition of biliary colic, which is term commonly used for both forms of gallstone colic, will be clarified in the manuscript.

Second, the Reviewer focuses on the nomenclature of two different patterns of liver enzyme elevation, namely elevations of aminotransferases and related hepatocellular enzymes that indicate hepatocyte damage or "Medical" liver injury, versus elevations of alkaline phosphatase, gammaglutamyl transferase, and related enzymes that usually indicate a pattern characteristic of biliary obstruction (i.e., a "Surgical" pattern) or Cholestasis. The Reviewer appreciates that the early phase of acute biliary obstruction by a gallstone, which is nominally a potentially "Surgical" condition, is characterized by aminotransferase elevation that is typically considered to be "Medical", i.e. Indicative of hepatocellular damage. The likely explanation for this apparent paradox is that there is indeed hepatocyte injury in the early phase of acute biliary obstruction even though liver biopsies done during acute biliary obstruction (looking for hepatitis and other forms of hepatocyte damage) have been unrewarding. See Nathwani RA, Kumar SR, Reynolds TB, Kaplowitz N. Marked Elevation in Serum Transaminases: An Atypical Presentation of Choledocholithiasis. Am J Gastroenterology 2005; 100: 295-298] This is now addressed in the manuscript.

The Reviewer also implies, that the use of the term "hepatocellular" enzyme elevation that is used in subacute and chronic liver injury, may be inappropriate in very early biliary obstruction, but this is incorrect as it is likely that the aminotransferase elevation of the early phase of acute biliary obstruction is indeed due to hepatocyte injury and enzyme leakage. It should be noted that if the acute obstruction becomes subacute or chronic, a cholestatic pattern will emerge after a few days. This is usually attributed to the different mechanisms underlying hepatocellular and cholestatic enzyme elevation. Hepatocellular enzyme elevation comes from leakage of cytosolic enzymes from damaged hepatocytes (see Nathwani reference above), whereas alkaline phosphatase elevation is due to enzyme induction (See :- Kaplan MM, Righetti A. Induction of rat liver alkaline phosphatase: the mechanism of the serum elevation in bile duct obstruction. J Clin Invest 1970;49:508-16, and Hatoff DE, Hardison WGM. Bile Acids Modify Alkaline Phosphatase Induction and Bile Secretion Pressure After Bile Duct Obstruction in the Rat. Gastroenterology. 1981;80:666-72 This has been shown in rats by pretreatment with protein synthesis inhibitors before biliary obstruction is performed experimentally, so that alkaline phosphatase elevation is prevented.

We acknowledge that the retrospective nature of this study is open to selection bias, and we therefore mention this now in the manuscript.

Second Peer Review: We very much appreciate this highly favorable review.

Third Peer Review: This distinguished and thoughtful Reviewer has many objections that we believe we can address. On the face of it, the criticism could have merit, namely that there should not be cystic duct or common bile duct stones present if gallstones are not detected concomitantly in the gallbladder. However, it is entirely conceivable (and indeed often the case) that the stones seen in the cystic or common duct, represent stones that have exited the gallbladder leaving none behind or leaving only microscopic stones or crystals. Gallstone formation is dynamic and begins as crystals, which themselves can cause biliary colic in the absence of macroscopic stones. Also, crystals left behind in the gallbladder can latter aggregate into stones. It is therefore not correct to state, as the Reviewer does, that there cannot be biliary colic without residual stones in the gallbladder. Whereas stones or crystals in the common duct are necessary for biliary colic to occur, the reverse is not necessarily true. In other words, not all common duct stones cause pain. As explained in the response to the First Peer Reviewer, it is common experience that the rise in aminotransferases that occurs in the very early phase of acute biliary obstruction can resolve even if the obstruction persists, to be succeeded by a rise in alkaline phosphatase a day or two later, as alkaline phosphatase enzyme synthesis comes into play. The Reviewer is correct in asserting that the disappearance of an impacted stone is unlikely to occur, but this does not preclude the normalization of aminotransferases, however counterintuitive that may be. Whereas the Reviewer correctly points out that aminotransferase elevation occurs in cholecystitis without choledocholithiasis, we were careful to exclude cases of cholecystitis in our study, and moreover, the aminotransferase elevation seen with cholecystitis is accompanied by fever and leukocytosis, and is usually slow to resolve and requires cholecystectomy. The reviewer is correct in implying that the findings in this study are not especially novel but it is the importance of the report that actually does make it attractive. It appears is that this phenomenon is seemingly not well-appreciated by many physicians who mistakenly conclude that cases such as these represent some form of acute liver (hepatocellular) injury, such as viral or drug-induced hepatitis, and they overlook a gallstone etiology that may require later surgical intervention, such as laparoscopic cholecystectomy. The Reviewer is correct in implying that in atypical cases, other causes of acute hepatocellular enzyme elevation must be sought, as mentioned in the manuscript. This author has certainly even seen cases of biliary colic in which there is concomitant acute viral hepatitis, which deserves appropriate serological and other investigation, since a confirmed diagnosis of acute hepatitis may well dictate a delay in surgical treatment.