Dear Distinguished Reviewers,

We appreciate the time and consideration you have given to our work. We are pleased that you have taken interest in our manuscript and we are grateful for the thoughtful reviews. We have carefully taken each of your comments into consideration and appreciate the suggestions to improve the presentation of our work. Please see our responses listed below in order:

Reviewer #1:

1. **Comment:** *This is a valuable review of a very rare entity combining the authors' clinical series with a systematic review of the literature. The resulting clinical classification of symptomatic heterotopic pancreas brings an additional value to the report. I support the publication of this valuable material.*

   Response: Thank you for your support for the publication of our work. We are pleased that you found our contribution meaningful to the body of knowledge regarding heterotopic pancreas.

Reviewer #2:

1. **Comment:** *Have you ever use tumor maker to detect the GI tract tumor ? The clinical manifestations of heterotopic pancreas may be asymptomatic; if symptomatic, it can manifest as abdominal pain, GI bleeding, intussusception, or pancreatitis. Additionally, when heterotopic neoplasm occurs, there may be a mild elevation in the serum amylase level or tumor markers.*

   Response: We appreciate your comments and suggestions. In our own practice, we do use biochemical markers such as amylase and lipase to help guide our diagnosis. Unfortunately, we found that the widespread use of serum markers was not as consistent in the literature. We were able to collect data from some of the studies which reported elevations in serum amylase or lipase but these were the minority of cases. We updated the manuscript to outline this fact more clearly. Please refer to changes listed below.

   "Of the patients with clinical and radiographic evidence of pancreatitis, only 50 reported cases (19%) reported elevations in biochemical markers such as serum amylase or lipase correlating with the clinical or radiographic evidence of pancreatitis."

   In regards to tumor markers, in our case series we only dealt with benign heterotopic pancreas. While adenocarcinoma within HP has been reported, we have not encountered this. We did review and report on cases of adenocarcinoma arising within heterotopic pancreas within our systemic review and listed this in Table 2. However, we did not find any specific listing of serum CA19-9 or CEA levels in these cases.

2. **Comment:** *Have you ever use enteroscopy for the the GI tract tumor ? Small intestinal heterotopic pancreas is usually difficult to diagnose preoperatively. In the past, most cases of small intestinal heterotopic pancreas were diagnosed in laparotomies or autopsies. Recently, a few cases of small intestinal heterotopic pancreas were diagnosed by deep enteroscopy or capsule endoscopy*.

   Response: Thank you for your insights. We did employ endoscopy frequently in our own series of patients. Standard esophagogastroduodenoscopy and endoscopic ultrasound were used in 4 out of the 6 symptomatic patients in the series at our institution and are reported in the case

description sections in the results. We also identified multiple cases in our systematic review which report endoscopic diagnosis and management (including resection) of heterotopic pancreas. Cases which underwent endoscopic evaluation and treatment were listed in Table 2. and Table 3. respectively. However, as this study focused on cases found within the upper gastrointestinal tract, we did not report on cases within the small bowel diagnosed by capsule endoscopy or balloon push enteroscopy.

3. **Comment:** *Do your study mention about other diagnositc methods for clinical symptoms ? Conventionally, surgical resection is the mainstay method for treating small intestinal heterotopic pancreas. However, endoscopic resection via deep enteroscopy is an alternative method*.

   Response: We appreciate your comments and we agree that improvement in the diagnosis of this lesion is paramount in the proper identification and determination of treatment. We include a brief write up of the imaging modalities including CT, MRI and barium swallow in the discussion section of our manuscript. Likewise, we include a discussion regarding the reported cases of endoscopically managed lesion identified in the literature. This is addressed in the discussion portion of the manuscript below.

   "As the majority of HP lesions are benign and do not involve the entire visceral wall, many are amenable to local or endoscopic resection. Overall, we identified 158 cases of local endoscopic resection in our series. The largest series was published by Zhou et al who reported endoscopic submucosal dissection in 78 symptomatic patients with good results[260]. In this series, the majority of patients had lesions located in the submucosa or lamina propria and were less than 1cm in size. Likewise, the series published by Zhong et al included 30 patients of which 90% were under 2cm in size[14]. Thus, an endoscopic approach is a reasonable intervention in pathologically confirmed HP, <2cm in size in the submucosa."

4. **Comment:** *Your reference may consider to add this paper as below, it may be helpful for your study A Rare Cause of Elevated Serum CA19-9. -Wei Chou 1, Kai-Po Chang 2, Yi-Hua Wu 3.Gastroenterology. 2021 Jan;160(1):31-32.*

   Response: We appreciate the reference suggestion to improve the breadth of the topic discussion. We have reviewed the recommended paper and we have included it into the body of our discussion. Please see the updated discussion with the reference below.

   "Further diagnostic workup may require biochemical evaluation of serum amylase, lipase or, in some cases, tumor markers and/or endoscopic investigation[260]."

5. **Comment:** *This Retrospective Cohort Study has good potential, but needs to clearly disclose which article are the source of the cases cited in the review. It should specify how many cases were contributed by each source article, which is currently lacking*.

   Response: We appreciate the comments above and the potential that you see in our manuscript. A summary of the cases provided by each source article was listed in Table 2. We agree that this is an important and necessary portion of the of results. We have modified portions of the results that reference Table 2 to more clearly explain the table and its listing. In

addition, we have expanded the table legend to highlight the information more clearlyand draw the reader's attention to it. Please see edits listed below.

"A summary of the clinical cases of HP was performed by individual publication and were tabulated for review in **Table 2."**

"Table 2. Summary of systematic literature review listed by publication, number of symptomatic cases, demographics and clinical symptoms."

Reviewer #3.

1. **Comment:** *In this study, the clinical manifestations of gastrointestinal ectopic pancreas were highly summarized and carefully analyzed, which is of certain value for clinical diagnosis. However, some of the most common clinical manifestations are not specific, so the reference value is limited. In addition, this study did not analyze the difference between different treatment methods and patients' prognosis*.

   Response: We appreciate the response and comments from this reviewer. Ultimately our goal was to summarize the clinical manifestations as presented in the published literature to improve the understanding of this disease process which is otherwise somewhat obscure and lacking in its general description. We agree that the categories of clinical symptoms are broad and not specific to this diagnosis alone. However, these results were limited to the information and level of detail provided in the various publications. A larger prospectively collected cohort study would obviously be more detailed and of greater clinical value, however, the rarity of this disease process makes this type of study challenging.

   We are also in agreement that a more descriptive comparison of treatment methods and results would be beneficial to help formulate guidelines for management of this disease process. We attempted to summarize the various treatment modalities (resection, endoscopic removal ect….) in Table 3. Unfortunately, our analysis of the success and prognosis of each modality was limited to the description in each of the publications and the method and length of follow up reported by each study. This is an area where further prospective study would be greatly served, however, the retrospective nature of this study limits this form of analysis. We have attempted to provide the most accurate description of treatment options and results possible based on the study design. We have updated several sections of the discussion that pertain to treatment of heterotopic pancreas and the results found in the literature. Please see the tracked changes in the manuscript. We have also restructured the legend of Table 3 to highlight these results which is listed below.

   Table 3. *Treatment of heterotopic pancreas. Listing of **s**urgical or endoscopic procedures performed for patients with symptomatic heterotopic pancreas by procedure*

Reviewer #4.

1. **Comment:** *Title: Clinical Classification of Symptomatic Heterotopic Pancreas of the Foregut: A Case Series and Systematic Review of the Literature This manuscript has reviewed HP and classified the common clinical manifestations. This issue is important and interesting. However, it will require some revision before publication. 1, The authors classified the common clinical manifestations of HP. Is this classification useful to make accurate diagnosis of HP and to reduce*

unnecessary surgical resection? In addition, how do the authors select treatment for each classification of HP?

Response: Thank you for the feedback provided on our work. The main goal of this study was to evaluate symptomatic cases of heterotopic pancreas and provide a broad overview of the clinical manifestations which is currently lacking in the literature outside of case reports and small series. To support this goal, we felt that distillation of the various reports from the literature into an organized classification may help improve the diagnosis of this lesion and help drive better treatment decisions. After reviewing the results of the systematic review, we conclude that many of the cases of this anomaly are misdiagnosed and undergo more aggressive interventional treatment than may be necessary. We incorporated these findings into our discussion along with some of our management practices, however, we agree that this is the most clinically impactful portion of our work and we added several revisions to the discussion to reflect that. Please see additions to the manuscript below.

"Characterization of symptomatic lesions is difficult due to the relative infrequency of this diagnosis and the variability in presentation. This often leads to misidentification and suboptimal management in many cases. Large volume studies characterizing the common presentation of HP are lacking and the aim of this study was to provide a conglomerate population to classify the typical clinical presentation within the foregut and aid in classification. With improved understanding and recognition of this disease process, clinicians can render more appropriate treatment decisions that may save patients morbidity from radical resection."

Dyspepsia Discussion:

"The majority of patients with HP and dyspeptic symptoms are initially misdiagnosed and managed with medical therapy designed for reduction of acid secretion. It is unclear whether traditional treatments for gastritis and PUD is beneficial in these patients. If the inciting physiology is chemical irritation from pancreatic secretions, then traditionally prescribed therapies for reduce acid secretion would be unlikely to help alleviate symptoms. In patients who develop mucosal ulceration there may be some plausible benefit that acid reduction may prevent ulcer progression once breakdown of the mucosal barrier has already occurred. However, it is not clear whether this can promote adequate ulcer resolution in the setting of HP or prevent future recurrent ulceration since acid secretion is not believed to be the causative factor for inflammation or ulceration in this setting[41]. There were few symptomatic patients in the reviewed studies who were managed with observation or medical therapy and long term follow up was lacking. The single patient treated with medical therapy at our institution (Case 6), demonstrated symptomatic improvement and to date, has not returned with recurrent symptoms over six years of observation. However, an adequate evaluation of medical management compared to surgical or endoscopic resection is lacking and further study is needed to evaluate the optimal treatment modality."

Pancreatitis Discussion:

"Conservative treatment may be successful in mild cases of this disease process. Investigation of the inciting etiology should be performed with cessation of alcohol or smoking when applicable. However, in patients with repeated episodes of abdominal pain, oral intolerance and vomiting (as in Case 1 above), surgical intervention may be required. When accurately diagnosed, drainage of the pseudocyst and local excision is typically adequate, however, as demonstrated in our series, most patients undergo a more extensive resection

when HP is not correctly identified as the source preoperatively[235]. However, in patients with recurrent groove pancreatitis or cystic degeneration of the duodenal wall more radical surgical intervention is often required. Groove pancreatitis often requires resection with pancreaticoduodenectomy in order to resolve recurrent flairs of pancreatitis and avoid complications such has duodenal structuring and necrosis of the pancreatic head. The largest series of patients with cystic groove pancreatitis and cystic degeneration of the duodenal wall was published by Rebours et al. and included 105 patients[25]. In this series, 18% resolved with observation, 43% resolved with medical therapy of which half of these required nutritional support and 39% required surgical intervention. The majority of patients underwent a pancreaticoduodenectomy (N=`17) with the remainder undergoing endoscopic cyst fenestration, biliary bypass or gastric bypass for symptom management[25]."

Gastrointestinal Bleeding Discussion:

Definitive management of major bleeding caused by heterotopic pancreatic lesions is primarily through resection. There is no clear role for the medical management in gastric bleeding related to HP. Even among those patients with bleeding related to gastric ulceration, traditional medical management for gastric ulceration is of questionable utility as the presumed etiology of mucosal ulceration is not related to acid secretion. However, there may be an argument that medical therapy may reduce the potential of gastric secretions to propagate ulceration in the setting of an already disrupted mucosal barrier from HP. In the setting of acute gastrointestinal bleeding, endoscopic therapies can be utilized to control hemorrhage but ultimately resection of the offending lesion should be considered. There have been reports of endoscopic submucosal dissection and resection of HP in patients with melena and chronic anemia[251,252]. However, surgical resection remains the preferred management of a bleeding mass in most cases. This may be achieved with localized partial gastrectomy or duodenectomy in the setting of small lesions and more extensive resection and reconstructions can often be avoided.

Gastric Outlet Obstruction Discussion:

"Definitive management involves gastric decompression with a nasogastric tube and surgical correction of the obstruction. Surgical resection in these scenarios will typically require a more extensive resection than local excision or wedge resection as lesions causing obstruction are typicall large (>2cm) and located at or near the pylorus or duodenum. Distal gastrectomy with a Billroth I, Billroth II or roux-en-y reconstruction are the most common operations performed for gastric lesions causing obstruction while partial duodenectomy or pancreaticoduodenectomy may be required in the obstructing lesion in the duodenum. If the lesion is small or associated with a large cystic component causing obstruction and the pathology of the lesion is definitively known prior to surgery, a less extensive resection can be accomplished with preservation of the pylorus[257]. In the case series published by Ayantunde et al, two out of three cases of gastric outlet obstruction underwent distal gastrectomy while one underwent an anterior gastrotomy and local resection of the submucosal lesion[28]. The majority of studies reviewed in the literature however, reported more formal surgical resection and reconstruction procedures[58,64,245,255]."

Reviewer #5:

1. **Comment:** *The scope of your study focuses on describing and characterizing the clinical manifestations for gastric and duodenal heterotopic pancreas, but the study's tile is enlarged with heterotopic pancreas of the foregut. I thought it might be appropriate and inaccurate. It would be nice to have clinical manifestations of other site of foregut, including the small bowel, colon, gallbladder, spleen, esophagus and mediastinum.*

   Response: Thank you for the comments above. We agree that the term "foregut"encompasses anatomy outside the stomach and duodenum and may be an inaccurate term to use in this title. We have made the changes listed below to the title. We also appreciate the suggestion to broaden the scope of the article to include the description of clinical manifestations of heterotopic pancreas in tissues outside the stomach and duodenum. We considered this in our original study description, however, this presented multiple challenges. First, heterotopic pancreas is a rare anomaly with the vast majority of cases occurring in the stomach and duodenum. While symptomatic cases have been reported in other tissues, these are extremely uncommon and we did not encounter these in our own experience. Secondly, while the literature review demonstrated a wide range of single case reports involving multiple different tissues of origin, the number and depth of cases lacked appropriate quality to provide an accurate review and symptomatic classification. In addition, we concluded that the focus of this review should be to bring a general knowledge of symptomatic heterotopic pancreas cases to the clinician by characterizing and describing the most common and typical manifestations of this anomaly to help aid in diagnosis and treatment decisions. While a broader review would certainly be interesting, we felt that attempting to describe all of the rare and obscure clinical symptoms of heterotopic pancreas throughout the body would convoluted and outside of the scope and aim of this paper.

   "Clinical Classification of Symptomatic Heterotopic Pancreas of the Stomach and Duodenum: A Case Series and Systematic Review of the Literature"

2. **Comment:** *The discussion part is confused and needed to be simplify and elaborate*.

   Response: We appreciate the feedback and comments from the reviewer. We have responded by editing portions of the discussion to reduce the length and simplify the discussion. Based on responses from other reviewers, we have also elaborated on several of the discussion topics to improve the details of the discussion. Please see tracked changes with links to the comment above throughout the discussion to review the changes.

3. **Comment:** *Your study actually did a lot of work, but as far as I know there are still some articles on imaging diagnosis or differential diagnosis that also included the symptoms of heterotopic pancreas, but why have you not included them? Will the inclusion of these results increase the sample size of your study?*

   Response: Thank you for the comments and suggestions**.** The reviewer comments on the selection of the studies to include in the systematic review which is an important aspect of the study design. In designing the systematic review, we adhered to the PRISMA guidelines and

held to a strict inclusion and exclusion criteria. All article abstracts were reviewed if they included the key words or phrases and were within our database search in the English language. Articles including reviews of imaging, endoscopy, differential diagnosis ect… were included if they met our inclusion criteria and contained symptomatic cases which were described in detail and contained the necessary individual case information to provide a comparable analysis. There were several published reports in the literature, as the reviewer alludes to, that referenced symptomatic cases but did not contain enough detailed information to be included in the analysis from comparison. Likewise, we excluded some publications which included cases already sited in other publications and described duplicate patients. These were excluded as to not falsely inflate our sample size. Adhering to our inclusion and exclusion criteria and following PRISMA guidelines, we arrived at the sample size reported. We admit that there are limitations in this form of literature analysis and understand that completely representative populations are hard to achieve in this setting, however, we feel that academically we have adhered to our study criteria and hope that this study reflects our dedication to the methodology.