Determinants of mortality and treatment outcome following surgical interventions for acute mesenteric ischemia

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Background: Acute mesenteric ischemia (AMI) is associated with high morbidity and mortality due in part to its diagnostic difficulty and operative challenges. The purpose of this study was to review our experience of surgical management in patients with this condition and to identify variables associated with adverse outcomes following surgical interventions.

Methods: Hospital records and clinical data of all patients undergoing surgical interventions for AMI were reviewed during a recent 12-year period. Clinical outcomes as well as factors influencing mortality were analyzed.

Results: A total of 72 patients (41 females, overall mean age 65 years, range 34 to 83 years) were included in the study. Thrombosis and embolism were the cause of AMI in 48 patients (67%) and 24 patients (33%), respectively. Abdominal pain was the most common presenting symptom (96%), followed by nausea (56%). Preoperative angiogram was performed in 61 patients (85%). All patients underwent operative interventions, which included thromboembolectomy (n = 22, 31%), mesenteric bypass grafting (n = 33, 46%), patch angioplasty (n = 9, 12%), reimplantation (n = 5, 7%), and endarterectomy (n = 3, 4%). Bowel resection was necessary in 22 patients (31%) during the initial operation, and second-look operation was performed in 38 patients (53%). Perioperative morbidity and 30-day mortality rates were 39% and 31%, respectively. Univariate analysis showed renal insufficiency (P < .02), age > 70 (P < .001), metabolic acidosis (P < .02), and symptom duration (P < .005), and bowel resection in second-look operations (P < .01) were associated with mortality. Logistic regression analysis showed age > 70 (P = .03) and prolonged symptom duration (P = .02) were independent predictors of mortality.

Conclusions: Elderly patients and those with a prolonged duration of symptoms had worse outcomes following surgical intervention for AMI. A high index of suspicion with prompt diagnostic evaluation may reduce time delay prior to surgical intervention, which may lead to improved patient survival. Aggressive surgical intervention should be performed as promptly as possible in patients once the diagnosis of AMI is made. (J Vasc Surg 2007;46:467-74.)
Clinical characteristics and comorbid conditions were compared between the mesenteric embolic and thrombotic groups. Statistical analysis was performed to determine the association between relevant risk factors and treatment mortality with Fisher exact test or Pearson $\chi^2$ test in categorical variables. Wilcoxon rank-sum test was used to test for differences in continuous variables. Kaplan-Meier method was used to assess survival rate. A multivariate model was analyzed with factors found to be significantly associated with mortality based on univariate analysis results. In all analyses we only considered variables with at least 80% of the data present or recorded. All statistical analyses were performed using a statistical software program (SAS Institute, Cary, NC). All values were expressed as mean ± SEM. Statistical significance was accepted with a $P$ value of less than .05.

**RESULTS**

Patient information and clinical presentation. During the study period, 72 patients (31 males and 41 females) were identified who underwent surgical interventions for AMI. The median age was 65 years (range 34 to 83). Etiology for AMI included thrombosis in 48 patients (67%) and embolism in 24 patients (33%). Relevant demographic characteristics and comorbid medical conditions are listed in Table I. It is noteworthy that patients with mesenteric embolism were older (72 years vs 64 years; $P = .04$) with a greater incidence of atrial fibrillation (46% vs 13%; $P = .02$) compared with the thrombotic group. There were two incidents of new onset atrial fibrillation, both in the group that presented with embolism. All the patients with chronic atrial fibrillation were on adequate anticoagulation.

Patients with acute mesenteric thrombosis had an increased incidence of chronic mesenteric ischemic symptoms compared with the embolic cohort (54% vs 6%; $P = .01$). There were no significant differences among the other medical comorbidities analyzed.

Abdominal pain was the most common presenting symptom that was documented in 94% of patients (Table II). Among our patient cohorts, 26 patients (36%) who presented with acute peritonitis were taken to the operating room for immediate exploration. Other common symptoms on presentation included nausea (38%), vomiting (38%), diarrhea (31%), and tachycardia (31%) (Table II).

**Laboratory and radiographic evaluation.** Pertinent laboratory studies are listed in Table III. More than 90% of the patients had abnormally elevated leukocyte counts, with a mean value of $21.4 \times 10^9$/ml. The second most
commonly encountered abnormal finding was elevated lactate level, which occurred in 88% of tested patients with a mean value of 3.3 mmol/L.

Plain radiographic x-ray studies of the abdomen were both nonspecific and nondiagnostic. A total of 49 patients (68%) were noted to have a pattern consistent with ileus. AMI was diagnosed predominantly and definitively on the basis of a biplanar aortic angiogram, which was performed in 61 patients (85%). Fifteen patients who had previous symptoms of intestinal angina and presented with acute peritoneal findings underwent angiogram in the operating room prior to abdominal exploration. We took this approach in order to rule out two or three vessel disease that would imply multiple vessel bypass and decrease the expected time. Based on arteriographic appearance, accurate diagnosis of mesenteric embolism and thrombosis was made in 15 patients (71%) and 35 patients (88%), respectively.

Abdominal computed tomography (CT) scans were diagnostic for AMI in 38 (58%) of 65 patients who underwent this evaluation, with the SMA occlusion as the identifying feature. Findings suggestive of compromised intestinal viability or bowel necrosis caused by AMI, such as thickened bowel wall, pneumatoses intestinalis, free peritoneal fluid, and severe bowel dilatation, were noted in 41 patients (63%). Taken together, 43 patients (66%) who underwent CT scan showed evidence of AMI or bowel ischemia possibly caused by AMI. Other diagnostic evaluations, which confirmed the diagnosis of AMI, included magnetic resonance angiography (MRA) (n = 4) and mesenteric duplex scan (n = 3).

**Surgical interventions.** The mean duration between the onset of AMI symptoms and surgical intervention was 16 hours (mean 0.5 to 21 hours). Late presentation in the emergency room (ER), as well as work up of the abdominal pain once they arrived at the ER accounted for the time delay in most of the cases. All patients were fully heparinized as soon as the diagnosis was suspected. A variety of surgical interventions were performed, which included autologous saphenous vein bypass grafting (n = 22, 31%), prosthetic bypass grafting (n = 11, 15%), mesenteric thromboembolectomy (n = 22, 31%), patch angioplasty (n = 9, 12%), mesenteric reimplantation (n = 5, 7%), and endarterectomy (n = 3, 4%). Mesenteric bypass grafting was performed in 29 patients with mesenteric thrombosis and four patients with mesenteric embolism. In contrast, all patients who underwent mesenteric thromboembolectomy had acute mesenteric embolism. Among the 33 patients who had mesenteric bypass grafting procedures, antegrade bypass was performed in 17 patients, in which the target vessels included celiac artery alone (n = 10), SMA alone (n = 15), hepatic artery (n = 5), or middle colic artery (n = 5). In those patients who underwent an isolated celiac artery bypass grafting, eight of them had an occluded SMA while the remaining two patients had severely calcified SMA that was not suitable for revascularization. All these ten patients responded clinically following celiac artery revascularization without recurrent mesenteric ischemic symptoms. In all patients who underwent an antegrade mesenteric bypass, the donor vessel was the supraceliac aorta. On the other hand, retrograde bypass was performed in 16 patients in which infrarenal aorta and iliac artery was used as the donor vessel in 10 and 6 patients, respectively.

Bowel resection due to bowel necrosis was necessary in 22 patients (31%). A second look operation was performed in 38 patients (58%). Among them, 11 patients underwent additional bowel resection while four patients had bowel resection only during the second abdominal exploration. The decision to perform abdominal re-exploration was based on clinical findings of marginally viable bowel during the initial operation. Preoperative peritonitis was present in 20 patients (91%) who underwent bowel resection. Primary intestinal anastomosis was performed in 10 patients (45%) who had bowel resection while the remaining 12 patients (55%) had either ileostomy or colostomy creation.

**Treatment outcome.** Perioperative complications occurred in 49 patients (68%). Pneumonia, renal insufficiency (creatinine >2.0 mg/dL), and sepsis were the most common complications, which occurred in 10 (14%), 8 (11%), and 7 (10%) patients, respectively. Other operative complications included prolonged intubation (>7 days, n = 6, 8%), cardiac complications (n = 5, 7%), prolonged postoperative ileus (>7 days, n = 5, 7%), gastrointestinal hemorrhage, (n = 4, 6%), urinary tract infection (n = 7, 10%), acalculous cholecystitis (n = 2, 3%), and stroke (n = 1, 1%). Tracheostomy was necessary in three patients due to respiratory-related complications, while hemodialysis was required in six patients due to renal failure. Among these patients with renal failure, three patients required temporary hemodialysis via permacath placement while the remaining three patients required long-term hemodialysis via forearm arteriovenous access. No difference in perioperative complication rate was found between patients who had bowel resection vs those who did not. Similarly, no difference in morbidity rate was noted in the types of bypass conduit used or in methods of mesenteric revascularization. Six patients had occlusion of the mesenteric arteries in the postoperative period, which was documented by computed tomography (CT) of the abdomen in four pa-

### Table II. Presenting symptoms in patients with acute mesenteric ischemia

<table>
<thead>
<tr>
<th>Abdominal symptom</th>
<th>No of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>69</td>
<td>96%</td>
</tr>
<tr>
<td>Nausea</td>
<td>40</td>
<td>56%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27</td>
<td>38%</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>26</td>
<td>36%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>31%</td>
</tr>
<tr>
<td>Tachycardia (HR &gt;100 bpm)</td>
<td>22</td>
<td>31%</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>20</td>
<td>28%</td>
</tr>
<tr>
<td>Fever</td>
<td>15</td>
<td>21%</td>
</tr>
<tr>
<td>Hematemesis</td>
<td>13</td>
<td>18%</td>
</tr>
<tr>
<td>Constipation</td>
<td>6</td>
<td>8%</td>
</tr>
<tr>
<td>Evidence of shock</td>
<td>4</td>
<td>6%</td>
</tr>
</tbody>
</table>

HR, Heart rate.
patients and duplex ultrasound in two patients. Among them, three patients died during the postoperative period, while two patients underwent repeat mesenteric revascularization with saphenous vein bypass grafting.

The overall 30-day perioperative mortality rate in our series was 26%. The mortality rate of patients with mesenteric thrombosis and embolism was 25% and 28%, respectively ($P = \text{NS}$). Four patients died either while still in the hospital or in a rehabilitation facility. Mortality was 14% in patients who underwent surgical interventions less than 12 hours following the onset of AMI symptoms. In contrast, significantly higher mortality was noted in those who underwent surgical interventions more than 12 hours following the onset of AMI symptoms ($75\%, P = .02$). Increased mortality was also noted in patients with preoperative lactate elevation greater than 2 mmol/L ($P = .02$) or leukocytosis of greater than 18,000 cell counts/mL ($P = .03$). Among those who required bowel resection, no difference in mortality rate was found among those who had bowel resection during the first abdominal exploration or second-look operation. Similarly, no difference was noted in the mortality rates when comparing those who underwent a second-look exploration with those who did not undergo a second-look operation, which was 31% and 33%, respectively. Elderly patients with age greater or equal to 70 years was associated with a greater mortality rate (43%) when compared with those younger than 70 years of age ($23\%, P = .01$). No difference in the ischemic time was noted in the elderly patient cohort, which was $17 \pm 6.3$ hours, when compared with the ischemic time of $16 \pm 8.7$ hours in those younger than 70 years of age.

Late deaths occurred in 23 patients (16 in the mesenteric thrombosis group and seven in the mesenteric embolism cohort). The causes of late death included coronary disease in seven cases, malignancy in four cases, recurrent mesenteric ischemia in four cases, stroke in four patients, and traumatic injury in one patient. Four patients died with unknown cause. Using Kaplan-Meier analysis, the survival rates were 58% and 28% at 5 and 10 years, respectively (Fig 1). The long-term patency rate of mesenteric revascularization is shown in Fig 2. For the purpose of patency analysis, the time of mesenteric vessel occlusion was estimated as the midpoint between the time of the most recent known patency and the time of documented mesenteric occlusion. Late mesenteric vessel occlusion was recorded in 16 patients. The overall long-term mesenteric vessel patency following surgical revascularization was 64% and 52% at 5 and 10 years, respectively.

### Risk factor analysis of mortality

Risk factor analysis of all demographic, preoperative, and intraoperative clinical data in relation to mortality was performed. No significant differences were found with regards to etiology, gender distribution, laboratory variables, physical examination, or diagnostic findings. Univariate analysis showed renal insufficiency ($P < .02$), age $>70$ ($P < .001$), metabolic acidosis ($P < .02$), and symptom duration ($P < .005$), and bowel resection in second-look operations ($P < .01$) were associated with mortality. Multivariable analysis of significant univariate predictors identified that age $>70$ and prolonged symptom duration ($>24$ hours) were independent predictors of mortality. Specifically, increased age is associated with greater mortality with a relative risk ratio of 3.64 (95% confidence interval [CI], 1.2 to 4.2; $P = .03$) and prolonged symptom duration is associated with greater mortality with a relative risk ratio of 4.62 (95% CI, 1.3-5.1; $P = .02$).

### DISCUSSION

Acute mesenteric ischemia is a morbid condition that has progressively become more prevalent in recent decades with a current estimated incidence of 1 in 1000 hospital admissions.\(^5,7,9\) In this study, which focused on the clinical outcome of patients who underwent surgical revascularization for AMI, mesenteric thrombosis remained the most common cause of AMI. In addition, the majority of our patients had no previous symptoms of intestinal angina. Our study confirmed the findings of others in that the nonspecific initial symptomatology makes diagnosis at an early stage challenging.\(^{16,17}\) Abdominal pain was by far the most common presenting symptom in our series, which was noted in 96% of patients. It is noteworthy that a significant portion of our patients, or 28%, had peritonitis with findings of gangrenous intestine during the abdominal exploration that necessitated bowel resection. This finding may suggest that the classically taught dictum of “pain out of proportion to physical findings” is probably overlooked.

#### Table III. Summary of laboratory findings at admission

<table>
<thead>
<tr>
<th>Serum laboratory parameter (normal value range)</th>
<th>No of patients who had the serum test</th>
<th>Mean value</th>
<th>Proportion of patients with abnormal lab (no and %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count (&lt;11 x 10^9/ml)</td>
<td>72 (100%)</td>
<td>21.4 x 10^9/ml</td>
<td>65 (90%)</td>
</tr>
<tr>
<td>Lactate level (&lt;2.0 mmol/L)</td>
<td>70 (97%)</td>
<td>3.3 mmol/L</td>
<td>64 (89%)</td>
</tr>
<tr>
<td>Creatinine (0.8 to 1.4 mg/dL)</td>
<td>72 (100%)</td>
<td>1.4 mg/dL</td>
<td>12 (17%)</td>
</tr>
<tr>
<td>Urea nitrogen (BUN) (7-18 mg/dL)</td>
<td>72 (100%)</td>
<td>18 mg/dL</td>
<td>17 (24%)</td>
</tr>
<tr>
<td>Hemoglobin (13.5-17 g/dL)</td>
<td>72 (100%)</td>
<td>12.3 g/dL</td>
<td>9 (13%)</td>
</tr>
<tr>
<td>Base deficit (&lt;-2)</td>
<td>69 (96%)</td>
<td>-4</td>
<td>41 (59%)</td>
</tr>
<tr>
<td>Creatine kinase (22-328 U/L)</td>
<td>60 (83%)</td>
<td>319 U/L</td>
<td>18 (30%)</td>
</tr>
<tr>
<td>Amylase (53-123 U/L)</td>
<td>68 (94%)</td>
<td>135 U/L</td>
<td>44 (65%)</td>
</tr>
<tr>
<td>AST (7-28 U/L)</td>
<td>65 (90%)</td>
<td>38 U/L</td>
<td>42 (65%)</td>
</tr>
</tbody>
</table>

AST: Aspartate aminotransferase.
and further emphasizes the importance of early diagnosis before bowel necrosis develops.

The diagnosis of AMI requires a variety of clinical factors, as there is not a single reliable serological or radiographic test to confirm the diagnosis of AMI. Several commonly utilized serological studies as shown in Table III, such as leukocytosis, elevated amylase level, or the development of high anion gap metabolic acidosis, are suggestive rather than pathognomonic of AMI. More recently, D-dimer has been found to increase within as little as 30 minutes from the onset of intestinal ischemia after ligation of the superior mesenteric artery in experimental animal models. A time-dependent increase in the D-dimer serum levels was shown in these experiments. A further clinical studies undoubtedly will be necessary in order to validate the diagnostic importance of this serological test in AMI.

For patients who do not present with catastrophic abdominal symptoms, imaging is of paramount importance. CT scanning is a diagnostic modality commonly utilized in patients who present with abdominal pain and has been reported to be sensitive in the diagnosis of mesenteric occlusion. Dynamic CT angiography with three-dimensional reconstruction is anticipated to add significantly to its diagnostic value. The use of multidetector raw CT angiography has been shown in animal models to offer a 94% positive predictive value, and its use appears promising in a clinical setting. We observed only 58% accuracy in the ability of CT scan to diagnose mesenteric ischemia. This is most likely due to equipment and software limitations as evidenced by the fact that most of the inaccurate CT readings were seen early in the 12-year span that our review covers.

Despite advances in the techniques of CT imaging, traditional digital subtraction arteriography remains of value for these patients who present at an early stage and for whom diagnosis is still uncertain. In addition, our experience indicates that performing angiography has several advantages and should be pursued in the operating room even in patients with clinical peritonitis. We found that when the culprit vessels are defined angiographically and confirmed intraoperatively, a more targeted approach towards reconstruction of the compromised vessels can be justified, therefore avoiding prolonged operative time. This is of particular value in patients with chronic disease, in whom multiple bypass grafts may be necessary; as well as in the unstable patient who will benefit from a single bypass procedure to the occluded vessel that has precipitated the acute episode. In addition, balloon angioplasty and stenting can be utilized in the occasional patient with hostile abdomen that makes dissection hazardous; or the patient with frank bowel necrosis and no available autogenous conduit. Based on our clinical experience, we have summarized a diagnostic and therapeutic algorithm in treatment patients with suspected AMI (Fig 3).

Endovascular management as the sole treatment modality in cases of AMI remains controversial, since assess-

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Fig 1. Long-term survival rate in patients undergoing surgical revascularization for acute mesenteric ischemia using Kaplan-Meier analysis.

Fig 2. Mesenteric vessel patency rate in patients undergoing surgical revascularization for acute mesenteric ischemia using Kaplan-Meier analysis.

Fig 3. Diagnostic and treatment algorithm in patients with suspected acute mesenteric ischemia.
ment of intestinal viability is crucial, and can only be achieved with abdominal exploration and direct bowel inspection. That point aside, it is important to recognize that endovascular treatment may play an alternative therapeutic role in patients with a prohibitive operative risk who do not have frank peritoneal signs on physical exam. These patients might benefit from mesenteric angioplasty and/or stenting followed by close observation. Based on these treatment principles, Boley and associates used arteriography and subsequent catheter-based interventions or transcatheter vasodilator therapy as the initial or sole therapy of AMI. Catheter-directed thrombolysis as well as percutaneous angioplasty have also been used with satisfactory results in the treatment of acute mesenteric embolism with short-term follow-up.

Once the diagnosis of AMI is suspected, the surgeon is faced with multiple therapeutic challenges, which includes assessment of intestinal viability, revascularization to prevent further small bowel loss, and resection of necrotic bowel if necessary. Revascularization is usually accomplished with open revascularization techniques, although endovascular strategies may also play a role as previously described. Thirty-one percent of patients in our series had intestinal necrosis at the time of initial operation and necesitated bowel resection. Embolectomy for patients with mesenteric embolism was performed through the root of the small bowel mesentery, which occurred in 31% of our patients. Among those who underwent mesenteric bypass grafting procedures, they were constructed in either an antegrade or retrograde orientation. Antegrade bypass is technically more challenging, but employs the supraceliac aorta as an inflow source, which is relatively devoid of atherosclerotic disease. The retrograde bypass is technically easier and faster to create and therefore advantageous for the individual patient with labile vital signs or obese body habitus. However, extensive iliac artery calcification and kinking of the graft are potential problems. Similar to our series, excellent results with either configuration have been reported using either approach by many studies. When possible, blood flow is restored to at least two mesenteric vessels to ensure complete revascularization and prevent future ischemic episodes, although some researchers advocated that bypassing the superior mesenteric artery alone is an acceptable alternative with equally good results.

In our patients who required mesenteric bypass procedures, prosthetic bypass graft conduit was used in 15% of cases, which represented our preferred graft conduit of choice because it avoided the theoretical risk of graft kinking in contrast to a vein graft conduit. However, this approach is contraindicated in the setting of intestinal necrosis or questionable bowel viability due to the possibility of graft contamination. Saphenous vein or rifampin-soaked polyester graft can be alternatively used for conduit in a contaminated field if autogenous conduit is not available. Assessment of visceral perfusion can be performed after reconstruction with a combination of clinical examination, palpation of small jejunal branches, and use of continuous wave Doppler or intravenous injection of fluorescein. Some of the perfusion disturbances detected at that time are in fact reversible; therefore, a positive finding with any of the above methods for assessment of intestinal viability does not negate the value of the second look operation. In an effort to preserve as much small bowel as possible, only frankly necrotic bowel is initially resected and a second look operation should be considered whenever possible. This therapeutic principle was followed in our study in which 38 out of the 45 patients who required bowel resection upon initial exploration were taken back to the operating room for a second look laparotomy. Aggressive strategy with a scheduled second look laparotomy for all the patients who are found to have necrotic bowel has been described. However, we did not find this treatment approach to be necessary in our experience.

In our study, the 30-day mortality rate following surgical revascularization in patients with AMI was 31%. Parameters associated with increased mortality included renal insufficiency, age, metabolic acidosis, symptom duration, and bowel resection in second-look operations, whereas further analysis of this data with logistic regression showed that age >70 and prolonged symptom duration to be independent predictors of mortality. Our findings were in agreement with those identified in other recent series. Some of those predictors are in fact interrelated; symptom duration is a variable that the clinician has control over, since it is closely linked to a delay in diagnosis and the time the patient spends in the emergency department or having unnecessary diagnostic tests. This represents an important timeline, during which incomplete resuscitation leads to the development of volume depletion, metabolic acidosis, and renal insufficiency. Even worse, time delay is associated with more exacerbated ischemia reperfusion response after blood supply to the viscera has been restored, that leads to release of oxygen and nitrogen derived free radicals. In addition, development of a local inflammatory response results in intestinal epithelial cell damage, whereas cytokine release produces systemic effects adversely affecting organs including the lungs, liver, heart, and the kidneys.

Admittedly, there are several limitations in our study, which were related to the retrospective nature of the study and their potential patient selection and treatment bias. Since only patients with recognized diagnoses were identified and analyzed, the mortality rate in our series undoubtedly underestimate the true fatality of this condition. Moreover, there was no treatment randomization; each patient received treatment depending on surgeon’s preference and in accordance with his/her individual anatomy and disease etiology. Collecting data in this manner may be of limited value, especially when it comes to outcome determinants. These factors may have led to non-causal correlations and limit the usefulness of these results, especially in light of a small patient population for a rather uncommon disease. Keeping these study limitations in mind, we believe that the findings of our study remains valuable because it underscores the importance of early diagnosis and prompt inter-
vention in cases of suspected AMI. In addition, our study demonstrates that an aggressive approach in the management of patients with AMI may improve the disheartening mortality rates associated with this condition.

CONCLUSION

In conclusion, contemporary management of AMI requires a high index of clinical suspicion that will prompt rapid surgical intervention followed by aggressive postoperative care to prevent multigland failure, and rapidly recognize the development of recurrent mesenteric ischemia. Older age, the presence of acidosis and renal failure, duration of symptomatology prior to intervention, and repeated bowel resection are variables associated with increased mortality. Long-term survival rate remains poor mainly because of associated comorbidities and the development of systemic inflammatory response with subsequent postoperative multi-organ failure. Until the development of more sophisticated diagnostic methods allow for easier identification of patients with AMI, rapid intervention in order to decrease the time of ischemia prior to reperfusion remains one of the most important determinants of favorable outcome.

AUTHOR CONTRIBUTIONS

Conception and design: PL, PK
Analysis and interpretation: PL, PK, DL
Data collection: DL, NB
Writing the article: PK, PL
Critical revision of the article: WZ, HS, TT
Final approval of the article: PL, PK, DL, JN
Statistical analysis: PK, PL, NB
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Overall responsibility: PL, PK

REFERENCES


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