Terlipressin and Albumin vs Albumin in Patients With Cirrhosis and Hepatorenal Syndrome: A Randomized Study

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Background & Aims: Hepatorenal syndrome is common in patients with advanced cirrhosis and constitutes a major problem in liver transplantation. There is no effective medical treatment for hepatorenal syndrome.

Methods: Forty-six patients with cirrhosis and hepatorenal syndrome, hospitalized in a tertiary care center, were randomly assigned to receive either terlipressin (1–2 mg/4 hour, intravenously), a vasopressin analogue, and albumin (1 g/kg followed by 20–40 g/day) (n = 23) or albumin alone (n = 23) for a maximum of 15 days. Primary outcomes were improvement of renal function and survival at 3 months.

Results: Improvement of renal function occurred in 10 patients (43.5%) treated with terlipressin and albumin compared with 2 patients (8.7%) treated with albumin alone (P = .017). Independent predictive factors of improvement of renal function were baseline urine volume, serum creatinine and leukocyte count, and treatment with terlipressin and albumin. Survival at 3 months was not significantly different between the 2 groups (terlipressin and albumin: 27% vs albumin 19%, P = .7). Independent predictive factors of 3-month survival were baseline model for end-stage liver disease score and improvement of renal function. Cardiovascular complications occurred in 4 patients treated with albumin alone and in 10 patients treated with terlipressin and albumin, yet permanent terlipressin withdrawal was required in only 3 cases.

Conclusions: As compared with albumin, treatment with terlipressin and albumin is effective in improving renal function in patients with cirrhosis and hepatorenal syndrome. Further studies with large sample sizes should be performed to test whether the improvement of renal function translates into a survival benefit.

Hepatorenal syndrome (HRS) is a characteristic form of renal failure that occurs in patients with advanced cirrhosis and is associated with a very poor outcome.1,2 Because of the lack of effective therapies, HRS has become a major issue in clinical practice. Moreover, in patients who are candidates for liver transplantation, HRS is a common cause of death before transplantation and is associated with an increased morbidity and reduced survival after transplantation.3–5 Therefore, there is a need for effective therapies in patients with cirrhosis and HRS.

HRS is the consequence of a severe vasoconstriction of the renal circulation that causes a marked reduction in renal blood flow and glomerular filtration rate.1,2 All attempts to induce renal vasodilatation by the administration of vasodilator drugs have been unsuccessful.6 It is currently considered that HRS is the final consequence of a marked vasodilatation of the splanchnic circulation secondary to an increased production of vasodilators in the splanchnic bed. As a result, the effective arterial blood volume is severely reduced, and there is compensatory activation of major vasoconstrictor systems, which are responsible for renal vasoconstriction.1,2,7,8 This pathogenic concept has modified the approach to therapy of HRS, and several studies have been reported assessing the efficacy of vasoconstrictors, particularly vasopressin analogues to improve effective arterial blood volume.9–14 These studies show that vasopressin analogues improve renal function in patients with HRS. However, the available information is limited because studies are either retrospective, have a small number of patients, or are not randomized. Therefore, the current study was undertaken to evaluate the effects of terlipressin on renal function and survival of patients with cirrhosis and HRS.

Patients and Methods

Study Population

A total of 67 consecutive patients with cirrhosis and HRS diagnosed between January 2002 and February
2006 in 9 university hospitals were evaluated for inclusion in the study. The study was approved by the investigational review board at each hospital, and patients or relatives gave written informed consent to participate. Inclusion criteria were as follows: (1) cirrhosis as diagnosed by liver biopsy or clinical, biochemical, ultrasound, and/or endoscopic findings; (2) HRS either type 1, as defined by previously established criteria, \(^1\) or type 2 with a serum creatinine greater than 175 \(\mu\)mol/L; (3) age 18 to 75 years; (4) absence of bacterial infection associated with findings of systemic inflammatory response as diagnosed by the presence of at least 2 of the following criteria: body temperature <36°C or >38°C, heart rate >90 beats/ min, respiration rate >20/min, and white-cell count <4 or >12 \(\times\) 10\(^9\)/L or >6% of band forms\(^1\); patients with bacterial infections, however, could be included in the study if renal failure persisted after infection resolution; (5) the absence of cardiovascular diseases and any extrahepatic disease that could affect the short-term prognosis; (6) the absence of findings suggestive of organic nephropathy; and (7) the absence of advanced hepatocellular carcinoma. \(^1\) Twenty-one of the 67 patients screened were not randomized for the following reasons: severe cardiovascular disease (n = 4), refusal to participate (n = 4), terminal condition (n = 4), advanced hepatocellular carcinoma (n = 3), sepsis (n = 2), and miscellaneous reasons (n = 4).

A total of 46 patients were randomly assigned to 1 of 2 groups: 23 to terlipressin plus albumin and 23 to albumin alone. Albumin was given in association with terlipressin because there is evidence that albumin improves the beneficial effects of terlipressin on HRS. \(^1\) Randomization was centralized in the Hospital Clinic of Barcelona and was done with the use of sealed opaque envelopes containing the treatment assignments, which were based on random numbers generated by the STATA statistical package (Stata Corp. 1999, 7.0, College Station, TX). Patients with type 1 HRS were randomized independently from those with type 2 HRS. A chart flow of patients included in the study is provided in Figure 1. The study was registered in Clinicaltrials.gov with the number NCT00287664.

**Study Protocol**

Before randomization, all candidate patients entered a screening period during which causes of renal failure other than HRS were excluded using criteria defined elsewhere. \(^1\) Diuretic agents were withheld during this period, and a trial of plasma expansion was given to rule out the existence of renal failure because of volume depletion. If after the screening period (median time, 3 days) renal failure persisted and patients met the criteria of inclusion, patients entered the study and were randomized to receive either terlipressin and albumin or albumin alone. Physical examination, chest x-ray, and routine laboratory tests were performed in all patients before the initiation of therapy and at regular intervals during treatment. In all patients included, albumin (Albumin 20 percent; Instituto Grifols, Barcelona, Spain) was given at a dose of 1 gram per kilogram of body weight during the first 24 hours, followed by 40 grams per day, targeted to obtain a central venous pressure (CVP) between 10 and 15 cm of water. CVP was measured at least once a day throughout the study period. When CVP increased over 15 cm of water, the albumin dose was reduced to 20 g/day and was withheld when CVP increased above 18 cm of water or there were clinical or radiologic signs of pulmonary edema. In addition, these patients received intravenous (IV) boluses of furosemide. In patients randomized to treatment with terlipressin and albumin, terlipressin (Glypressin, Ferring AB, Sweden) was administered initially at a dose of 1 mg/4 hour as IV bolus for 3 days. If after the first 3 days serum creatinine had decreased at least 25% of the pretreatment values, the dose was not modified. In patients in whom serum creatinine had not decreased at least 25% of the pretreatment values within the first 3 days, the dose was increased to a maximum of 2 mg/4 hour. Terlipressin was given until serum creatinine had decreased below 133 \(\mu\)mol/L or for a maximum of 15 days. Terlipressin administration was withheld if patients developed signs or symptoms compatible with ischemic complications. An amendment was made during the study to allow treatment with terlipressin in patients assigned to albumin therapy who were potential candidates to liver transplantation if there was no improvement in renal function after 7 days. This amendment was requested by several institutional review boards on the basis of published studies reporting a reversal of HRS in patients treated with terlipressin. \(^1\) Patients were admitted to the intensive care unit if they developed a severe complication of cirrhosis, had hemodynamic instability, or required ventilatory support. The majority of patients was hospitalized in a general hepatology ward. Complications of cirrhosis developing during the study in patients from both groups were treated accordingly.

![Flow chart of patients included in the study.](image-url)
to standardized therapeutic measures. Briefly, patients with gastrointestinal bleeding because of esophageal varices were treated with endoscopic therapy, particularly band ligation; bacterial infections were treated empirically with IV ceftriaxone or other antibiotics according to the results of cultures; hepatic encephalopathy was treated with lactulose and rectal enemas. No prophylactic antibiotics were given except for patients with previous history of spontaneous bacterial peritonitis who received oral norfloxacin 400 mg/day (8 patients in each group). After discharge, patients were followed at regular intervals for 3 months. Patients treated with transjugular intrahepatic portosystemic shunt or undergoing transplantation during follow-up were considered censored at time of the intervention for survival analysis.

**Statistical Analysis**

The primary outcomes were survival at 3 months and improvement of renal function, defined either as complete response when there was a reduction in serum creatinine below 133 μmol/L during treatment or partial response when there was a reduction in serum creatinine of greater than 50% of the pretreatment value but with an end-of-treatment value equal to or greater than 133 μmol/L. Sample size was calculated according to survival at 3 months. Assuming a 3-month survival rate of patients with HRS treated with terlipressin and albumin of 35%9–11 and a survival rate of 5% in the control group,19,20 a minimum of 50 patients per group was required to allow a detection of a difference of 30% between the 2 groups, considering a “drop-out” rate of 15%, with a 2-sided type I error of 5% and a type II error rate of 20%. The final analysis was conducted on an intention-to-treat basis. Comparisons between groups were performed with the use of the χ² test or Fisher exact test for categorical data and Mann-Whitney and Wilcoxon tests for continuous data. The same univariate analyses were also used to identify factors predictive of 3-month survival and of response to therapy. Multivariate analyses were done using stepwise forward logistic regression. Probability curves were constructed using the Kaplan-Meier method and compared with the log-rank test. Calculations were performed with the SPSS 14.0 (SPSS, Chicago, IL). Results are presented as mean ± SD. All reported P values are 2-tailed, and values less than .05 were considered statistically significant.

**Results**

**Baseline Characteristics of the Patients**

There were no significant differences between the 2 groups in clinical and laboratory data at enrollment (Table 1). Both groups were also similar with respect to the percentage of patients with type 1 HRS (74% in the terlipressin and albumin group vs 78% in the albumin group). Twelve patients in the terlipressin and albumin group and 8 patients in the albumin group had an infection as the precipitating event of HRS (spontaneous bacterial peritonitis in 5 and 2 patients, respectively).

**Renal Function**

Improvement of renal function was significantly more frequent in patients randomized to treatment with terlipressin and albumin than in patients randomized to albumin infusion alone: 10 out of 23 patients (43.5%), 9 with complete response, compared with 2 out of 23 patients (8.7%), 1 with complete response, respectively (P = .015). Out of the 10 patients who responded to terlipressin and albumin, 6 had type 1 HRS, and 4 had type 2 HRS. In this group, the rate of response in patients with type 1 HRS was 35% (6 out of 17 patients), whereas that of patients with type 2 HRS was 67% (4 out of 6 patients) (P = .34). The 2 patients who responded to treatment in the albumin group had type 1 HRS (response rate, 11% in type 1 HRS). There were no significant differences between the 2 groups with respect to the duration of randomized treatment (7 ± 5 days in the terlipressin and albumin group vs 8 ± 5 days in the albumin group, P = .741). The cumulative albumin dose given was greater in patients assigned to albumin alone compared with that of patients assigned to terlipressin and albumin (275 ± 176 vs 190 ± 213 g, P = .015).
Figure 2 shows the probability of achieving improvement of renal function in patients from both groups. Out of the 10 patients who responded with terlipressin and albumin, 7 had response with a dose of terlipressin of 1 mg/4 hour and 3 patients with 2 mg/4 hour. In patients who responded to treatment with terlipressin and albumin, serum creatinine decreased from 256 ± 71 to 115 ± 18 μmol/L (P = .005) and mean arterial pressure increased from 75 ± 13 to 84 ± 18 mm Hg (P = .02). No significant changes were observed in these parameters in patients who did not respond to treatment with terlipressin and albumin (362 ± 195 vs 433 ± 248 μmol/L and 68 ± 10 vs 69 ± 12 mm Hg, respectively; P = ns for both). In the 2 patients who showed an improvement of renal function in the albumin group, serum creatinine decreased from 409 to 150 and 230 to 106 μmol/L, respectively. No significant changes in renal function or systemic hemodynamic parameters were observed in patients treated with albumin who did not respond to therapy. To assess whether the number of patients included by center could have had an influence on response to therapy, the rate of response in centers that included 5 or more patients (3 centers) was compared with that of centers that included less than 5 patients (6 centers). Rate of response to terlipressin and albumin was 43% (6 out of 14 patients) and 44% (4 out of 9 patients) in both groups of centers, respectively (P = 1.0). Corresponding values in the albumin group were 8% (1 out of 13 patients) and 10% (1 out of 10 patients), respectively (P = 1.0).

In the whole series of patients, predictive factors of response to therapy were etiology of cirrhosis, baseline serum bilirubin, leukocyte count, serum creatinine and urine volume, and treatment assignment. In multivariate analysis, the independent predictive factors of response to therapy were baseline urine volume, serum creatinine and leukocyte count, and treatment assignment (Table 2). Of the 10 patients who responded to terlipressin plus albumin, only 1 patient (10%) had recurrence of renal failure 18 days after terlipressin withdrawal. Eleven of the 23 patients assigned to albumin received terlipressin after treatment with albumin, and 1 of them had improvement of renal function.

**Survival**

There were no significant differences between the 2 groups with respect to the number of patients who were alive at 3 months, 6 in the terlipressin and albumin group (27%) and 4 in the albumin group (19%) (P = .7). Causes of death were similar in the 2 groups. In patients included in the terlipressin and albumin group, causes of death were multiorgan failure (n = 11), liver failure (n = 2), acute respiratory distress syndrome (n = 1), hepatorenal syndrome (n = 1), and unknown (n = 2). In patients in the albumin group, causes of death were multiorgan failure (n = 7), liver failure (n = 6), sepsis (n = 2), hepatorenal syndrome (n = 1), and unknown (n = 1). A univariate analysis of survival showed that baseline serum bilirubin, prothrombin time, serum creatinine, serum sodium, heart rate, leukocyte count, Child–Pugh score, and model for end-stage liver disease (MELD) score and response to therapy were associated with prognosis. In multivariate analysis, independent predictive factors of 3-month survival were only baseline MELD score and response to therapy (Figure 3).

**Adverse Events**

Table 3 shows the adverse events observed in both groups during randomized treatment. There was a similar incidence of hepatic encephalopathy, bacterial infections, and gastrointestinal bleeding in both groups. One patient in the terlipressin and albumin group developed a myocardial infarction, abdominal signs compatible with intestinal ischemia, and circulatory overload. Two patients developed abdominal signs suggestive of intestinal ischemia, in 1 of them associated with circulatory overload. Two other patients developed transient arrhythmia: 1 patient bradycardia and another patient ven-
tricular extrasystolia that did not require permanent treatment discontinuation. However, in 1 of these patients, terlipressin treatment was later discontinued because of high arterial pressure values. Finally, 9 patients (5 in the terlipressin and albumin group and 4 in the albumin group) developed signs of circulatory overload, which improved after temporary suppression of albumin together with furosemide administration and did not require permanent treatment discontinuation. Taken together, cardiovascular complications (myocardial infarction, intestinal ischemia, and/or circulatory overload) occurred in 10 patients in the group treated with terlipressin and albumin compared with 4 patients in the group treated with albumin (Fisher exact test, $P = .108$).

Discussion

The main finding of this randomized comparative study is that the administration of terlipressin, a powerful vasoconstrictor drug acting through V1 vasopressin receptors, together with albumin is effective in improving renal function in patients with cirrhosis and HRS. In fact, renal function improved in 43.5% of patients treated with terlipressin and albumin compared with only 8.7% of control patients treated with albumin alone ($P = .017$). This indicates that HRS is reversible by pharmacologic treatment, at least in a significant proportion of patients, and provides indirect confirmation of the crucial role of arterial vasodilation in the pathogenesis of this condition. In patients treated with terlipressin and albumin, the response rate was higher in patients with type 2 HRS compared with that of patients with type 1 HRS (67% vs 35%, respectively), although the difference was not statistically significant perhaps because of the limited number of patients with type 2 HRS included in the study. The improvement of renal function was associated with a significant increase in arterial pressure, whereas no increase in arterial pressure was observed in patients who did not respond to therapy. These data are consistent with the existence of a major relationship between circulatory and renal function in patients with HRS and suggest that an impaired vascular response to vasoconstrictors may account, at least in part, for the lack of improvement of renal function in patients with HRS treated with terlipressin and albumin who did not respond to therapy. Nevertheless, other possibilities for lack of response to therapy should be considered. First, in

Table 3. Adverse Events During Randomized Treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>Terlipressin + albumin, n = 23 (%)</th>
<th>Albumin, n = 23 (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic encephalopathy (n)</td>
<td>16 (70)</td>
<td>16 (70)</td>
<td>.538</td>
</tr>
<tr>
<td>Bacterial infection (n)</td>
<td>9 (39)</td>
<td>12 (55)</td>
<td>.23</td>
</tr>
<tr>
<td>Gastrointestinal bleeding (n)</td>
<td>4 (17)</td>
<td>6 (26)</td>
<td>.722</td>
</tr>
<tr>
<td>Myocardial infarction (n)</td>
<td>1 (4)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Suspected intestinal ischemia (n)</td>
<td>3 (13)</td>
<td>0</td>
<td>.233</td>
</tr>
<tr>
<td>Arhythmia (n)</td>
<td>2 (9)</td>
<td>0</td>
<td>.489</td>
</tr>
<tr>
<td>Circulatory overload (n)</td>
<td>7 (30)</td>
<td>4 (17)</td>
<td>.187</td>
</tr>
<tr>
<td>Arterial hypertension (n)</td>
<td>1 (4)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Other (n)</td>
<td>7 (30)</td>
<td>2 (9)</td>
<td>.135</td>
</tr>
</tbody>
</table>

- Associated with myocardial infarction in one patient.
- Associated with radiologic signs of pulmonary edema in 4 patients treated with terlipressin and albumin and in 1 patient treated with albumin alone.
- Associated with radiologic signs of pulmonary edema in 4 patients treated with terlipressin and albumin and in 1 patient treated with albumin alone.
- Associated with radiologic signs of pulmonary edema in 4 patients treated with terlipressin and albumin and in 1 patient treated with albumin alone.
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Figure 3. Probability of survival at 3 months of patients included in the study, classified according to improvement of renal function during randomized treatment (left graph) and base-line model for end-stage liver disease (MELD) score (right graph). MELD score could not be calculated in 2 patients.
the whole series of patients, independent predictive factors of response were baseline serum creatinine, urine volume, and leukocyte count. This raises the possibility that the severity of renal failure and the existence of systemic inflammatory response at the time of initiation of therapy could have an important influence on the reversibility of HRS and/or effectiveness of therapy. Second, although all patients included in the study were carefully evaluated with respect to the etiology of renal failure and all met the internationally accepted diagnostic criteria of HRS, the possibility that renal failure in some patients was not due to HRS cannot be ruled out completely because there is no specific diagnostic test available currently to verify the diagnosis of HRS. Finally, recent studies have provided evidence suggesting that an impairment of cardiac function plays a role in the pathogenesis of HRS. Therefore, although not evaluated in this study, the possibility exists that an associated impairment of cardiac function could account, at least in part, for lack of response in a proportion of patients treated with terlipressin and albumin. This suggestion deserves investigation in future studies.

Recent studies have shown that vasoconstrictors other than terlipressin, such as α-adrenergic agonists, particularly noradrenaline or miodrione, improve renal function in patients with HRS. However, the number of studies is very limited and includes low numbers of patients. Large, comparative studies between terlipressin and noradrenaline or midodrine are therefore needed to answer the question of whether other vasoconstrictors have similar efficacy to that of terlipressin.

The possibility of improving renal function in patients with HRS may be particularly relevant in patients awaiting liver transplantation. The presence of HRS at the time of transplantation is associated with an increased morbidity and mortality after transplantation. Therefore, the administration of terlipressin and albumin could be useful in these patients because the improvement of renal function before transplantation may lead to an improved posttransplantation outcome. Nevertheless, studies should be performed to assess specifically the beneficial effects of treatment with terlipressin and albumin in the transplant population.

The current study showed no significant differences in 3-month survival in the 2 treatment groups: 27% in the terlipressin and albumin group vs 19% in the albumin group (P = .7). It is important to note that, whereas the observed survival in the terlipressin and albumin group was only slightly lower than that expected on the basis of previous data from noncontrolled studies with vasopressin analogues, the observed survival in the control group (19%) was much higher than that previously reported (5%). In these latter studies, patients with HRS either did not receive treatment or were treated with dopamine or peritoneovenous shunting, procedures that are known to have no effect on renal function or survival. The relatively high 3-month survival observed in the control group of the current study was therefore unexpected and is difficult to explain. One possible explanation is that the administration of albumin has beneficial effects on the natural history of patients with advanced cirrhosis that could be related to some of the intrinsic properties of albumin, such as its antioxidant effects and/or its high capacity to bind substances that may have deleterious effects on organ function in patients with liver diseases, such as nitric oxide-related compounds, endotoxin, or cytokines. Along these lines, few recent randomized, controlled studies have shown that the administration of albumin or treatment with albumin dialysis reduces the incidence of complications and/or improve survival in patients with advanced cirrhosis. With a 3-month survival difference of 8% between the 2 groups observed in the current study (27% in the terlipressin and albumin group vs 19% in the albumin group), the estimated sample size required to demonstrate a significant difference in survival in favor of terlipressin and albumin was of 431 patients per group. Considering that this sample size would have been impossible to achieve within a reasonable period of time, the current study was terminated after the inclusion of approximately half of the calculated sample size.

The independent predictors of survival in the whole series of patients were the improvement of renal function during treatment and baseline MELD score. In patients who responded to therapy, 3-month survival probability was 58% compared with 15% in patients who did not respond to therapy (P = .003) (median survival time greater than 90 days vs 13 days, respectively; P = .003) (Figure 3). This observation confirms findings from previous studies also pointing toward an association between response to therapy and improved survival and underscores the important contribution of renal failure to the poor outcome of patients with cirrhosis and HRS. The difference in median survival time between responders and nonresponders, although small in relative terms, may represent a crucial survival advantage in specific conditions, particularly patients who develop HRS while awaiting transplantation or potential candidates to liver transplantation who are not yet listed.

The adverse events observed in patients included in the current study deserve specific comments. First, the population of patients with HRS is a very labile population of patients because of the existence of extremely severe organ dysfunction, not only in the liver and kidneys but also in other organs such as heart, systemic arterial circulation, and brain. Therefore, these patients are prone to develop many severe complications. Second, terlipressin is a powerful vasoconstrictor with effects on several vascular beds because of its action on vasopressin V1 receptors present in vascular smooth muscle cells of the arterial wall. Although its safety profile is better than that of other vasopressin analogues, adverse effects on cardiovascular function have been reported during terlipressin administration. In the current study, 10 patients treated with terlipressin and
albumin developed adverse effects on cardiovascular function, including myocardial ischemia, arrhythmia, intestinal ischemia or circulatory overload, compared with 4 patients treated with albumin alone who developed circulatory overload. When circulatory overload was excluded, the number of patients who developed cardiovascular complications in both groups was 5 (22%) and 0, respectively. Therefore, patients with HRS treated with terlipressin should be submitted to a close clinical surveillance, together with cardiac monitoring, ideally in semi-intensive or intensive care unit, and if signs of ischemia develop, terlipressin should be discontinued promptly. Finally, because of the administration of albumin, patients should also be evaluated closely during treatment for early recognition of signs of circulatory overload.

The current study has some limitations that should be mentioned. First, as indicated previously, the sample size was not sufficient to demonstrate a significant improvement in survival. Second, ideally, the study should have been performed using a double-blind design. However, this was not possible because our study was not sponsored by a pharmaceutical company and hospital pharmacy services cannot comply with the strict European legislation for preparing double-blind placebo medication for studies sponsored by investigators independent from the medical industry.

In conclusion, the results of this randomized, comparative study indicate that terlipressin and albumin are effective in improving renal function in patients with cirrhosis and HRS compared with albumin administration alone. No significant effect of terlipressin and albumin therapy on survival was found. Nevertheless, given the lack of alternative therapies for HRS, the administration of terlipressin and albumin should be considered for the management of patients with cirrhosis and HRS, particularly in patients who are candidates to liver transplantation.

Appendix

List of Other Investigators of the Terlipressin and Albumin for Hepatorenal Syndrome Study (TAHRS) Trial

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References


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M.M.-L. and M.N.P. contributed equally to this work.