Advancements in imaging modalities have revolutionized the diagnosis of ruptured cerebral aneurysm. In the past, detecting aneurysms generally required the use of DSA, but CTA offers several advantages. It is less time consuming and can be performed immediately after the noncontrast CT diagnosis of spontaneous SAH. In addition, CTA clearly demonstrates the topography of most aneurysms in the presence of an acute hemorrhage. It is therefore helpful in localizing a ruptured aneurysm under emergency conditions and, currently, is often used as the first step for evaluation and planning of therapeutic interventions.

Active bleeding from an aneurysm after an episode of SAH is recognized as a life-threatening event. Hyperacute rebleeding within 3 or 6 hours after the initial SAH has been estimated to occur in 35.9% and 48.6% of patients, respectively, and the mortality rate in patients who experience such aneurysm rerupture is approximately 60.2%. Within the spectrum of patients with reruptured aneurysms, those with active contrast extravasation during imaging represent a distinct subgroup. Extravasation of a ruptured aneurysm during DSA is not unusual, and it is generally associated with a poor outcome. In DSA-based clinical studies, the incidence of active extravasation during imaging is 3.1%–8.7%, and poor outcome is observed in approximately 83% of these patients. To avoid SAH-related rebleeding and its associated high mortality...

Hyperacute cerebral aneurysm rerupture during CT angiography

Clinical article

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Object. The object of this study was to identify the clinical features and outcomes of a subgroup of patients with aneurysmal subarachnoid hemorrhage (SAH) who had active contrast extravasation from a ruptured aneurysm during initial cerebral CT angiography (CTA).

Methods. The authors performed a retrospective study of spontaneous SAH cases involving patients treated at their institute. They identified 9 cases in which active contrast extravasation was evident on the initial CT angiogram. Another 12 similar cases were also identified in a literature review and data was gathered from these cases to evaluate the outcomes.

Results. Analysis of all 21 cases revealed that the overall outcomes in cases characterized by active aneurysmal bleeding during CTA were poor. Seventy-six percent of patients had unfavorable results. Patients who showed poor neurological status at presentation died no matter what kind of treatment they received. In contrast, patients who presented with good neurological status initially had a chance of favorable outcome. Among the patients with good initial neurological status, most demonstrated rapid deterioration of their condition during the CTA examination; only those who received immediate and effective decompressive surgery and aneurysm obliteration had good results.

Conclusions. Active aneurysmal rebleeding during CTA is an uncommon but devastating event. Though the mortality of this distinct group of patients remains high, a clinical subgroup may benefit from immediate surgery. Patients with good initial neurological status who show rapid neurological deterioration may still have a favorable outcome if they undergo timely and successful decompressive surgery and proper aneurysm obliteration. Patients who present with poor neurological status do badly, and there is no effective treatment for such patients.

Key Words • aneurysm • subarachnoid hemorrhage • computed tomography • angiography • vascular disorders

Abbreviations used in this paper: CTA = CT angiography; DSA = digital subtraction angiography; GOS = Glasgow Outcome Scale; mRS = modified Rankin Scale; SAH = subarachnoid hemorrhage; WFNS = World Federation of Neurosurgical Societies.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
rate, some authors propose that intraarterial angiography should not be performed in the early period after the ictus, but this would mean delaying any surgical intervention until after DSA can be performed.

Since the introduction of CTA, however, earlier surgical intervention has become more feasible. Because CTA can be accomplished more rapidly, the pretreatment evaluation time is reduced. It is also commonly believed that CTA cannot cause rebleeding. Thus, favorable outcomes seem possible.

No large series of cases involving this distinct group (patients with active extravasation during CTA) have been reported. Several papers have been published on the topic, but they consist of sporadic reports of one or a few cases. The objective of the present retrospective study is to describe the treatment outcome of this special disease entity and to identify a subgroup of patients who might have a favorable outcome following appropriate treatment—a subgroup that has not been described in previous reports.

Methods

Study Design

We performed a retrospective review of 62 cases of aneurysmal SAH involving patients treated in our institution between January 2006 and August 2007. In all cases, the SAH was spontaneous, without any history of trauma. Ruptured aneurysms were confirmed by reviewing the medical records, surgical charts, and all imaging studies. At presentation, the clinical characteristics of the patients, including sex and age, were recorded. All patients were classified according to the WFNS grading system after an initial resuscitation in the emergency department.

Subarachnoid hemorrhage was diagnosed in all cases on the basis of an initial noncontrast CT examination within 1 h after arrival at the emergency department and was graded according to the Fisher scale (Grade 1, no evidence of hemorrhage; Grade 2, SAH with thickness < 1 mm; Grade 3, SAH with thickness ≥ 1 mm; and Grade 4, SAH of any thickness with intraventricular hemorrhage or parenchymal extension). A CTA examination was performed when vascular abnormalities were suspected. The diagnoses of aneurysms were usually straightforward when subarachnoid blood was filtered out by manipulating the window and level of the CTA imaging. However, in the presence of unsatisfactory definition of aneurysm or adjacent vasculature, a complementary DSA examination was arranged for further delineation. The intervals from the ictus to CTA and operation were specifically analyzed.

Imaging Protocol

All patients enrolled in this study were examined using the same CT unit (VCT, GE Healthcare). Venous routes were created at cubital veins (either side, according to accessibility) for patients undergoing CTA. A bolus test was performed at the level of the ascending aorta with 12 ml of contrast medium (Ultravist 370, Bayer) followed by 16 ml of normal saline at a rate of 4 ml/second; CTA was then performed with 60 ml of contrast medium followed by 40 ml of normal saline at the same rate. Helical mode with 32 * 0.625 collimation, 0.969 pitch, 0.4-second rotational time, and 100 kVp was used; 200 mA was used for imaging without contrast medium, and 400 mA was used for contrast-enhanced imaging. The coverage was from aortic arch to vertex. To minimize patient movement, the precontrast scan was obtained simultaneously during contrast material injection, and the postcontrast scan was obtained after a delay time according to the bolus test before CTA. Subtraction images were then obtained with the corresponding precontrast and postcontrast arterial-phase source images (0.625 mm of section thickness).

Imaging Postprocessing

The subtracted CTA source images were loaded into a workstation (Advanced Workstation 4.3, GE Healthcare) for postprocessing. Multiplanar reformation, maximum intensity projection, and 3D volume rendering of images were performed by a radiologist to evaluate the intracranial vessels.

Diagnosis of Active Extravasation During CTA

The diagnosis of active extravasation from a ruptured aneurysm was demonstrated by the presence of contrast medium in the extravascular space on CTA. In some cases, the CT scan was repeated immediately after the CTA series to demonstrate whether contrast medium was retained in the extravascular space. The attenuation must be as high as that within the internal carotid artery after filtering out the signals of subarachnoid hematoma. The contrast can either localize adjacent to a ruptured aneurysm or extend distantly. All of the imaging results were confirmed by neuroradiologists.

Patient Management

After a diagnosis of ruptured aneurysm, patients were treated with iso- and hypertonic fluid to maintain a central venous pressure of 8 mm Hg or higher. The choice of surgical interventions as well as their timing depended on the neurosurgeon’s clinical judgment. Once rebleeding is identified, management of the patient’s deteriorating condition is challenging. Lowering the blood pressure may decrease the cerebral perfusion, and elevating blood pressure may accelerate aneurysmal bleeding. Our principal was to lower systolic blood pressure by 30 mm Hg, but not lower than 140 mm Hg, by administering 100–200 ml of mannitol and infusing nicardipine. Patients were then immediately transferred to the operating theater. Following surgery, all patients were admitted to the neurosurgical intensive care unit for postoperative monitoring. Vasopressors were administered if necessary after aneurysm obliteration to maintain a systolic blood pressure of more than 140 mm Hg. Transcranial Doppler ultrasonography was performed every day. If vasospasm worsened or there were clinical signs of ischemia, a CT perfusion study was performed. Cerebral angiography was then used to determine the degree of vasospasm; in the presence of severe vasospasm, intraarterial injection of nimodipine was performed by a neuroradiologist.
Outcome Analysis

The daily hospital course was followed using standard documentation, and the patients' outcomes were assessed using GOS and mRS scores at 6 months and 12 months, if feasible. Good outcomes were defined as a GOS score of 5 or 4 or an mRS score of 1 or 2, while other scores corresponded to poor outcomes.

Results

Clinical Characteristics of Patients With Aneurysm Rerupture During CTA

Among the 62 consecutive patients with ruptured aneurysms, 9 experienced rebleeding during CTA. This incidence was approximately 13%. Eight of 9 patients were female, and 1 was male. Their ages ranged from 34 to 85 years (mean 59 years). The clinical characteristics, treatment options, and outcomes of these cases are summarized in Table 1.

The severity of neurological status at presentation was rated as WFNS Grade II in 5 patients and Grade IV or V in 4. The Fisher scale grade based on the initial non-contrast CT scan was 4 in all cases. All of these patients underwent CTA following the diagnosis of SAH, with the interval between ictus and CTA ranging from 30 to 120 minutes (mean 70 minutes). All 5 patients who presented with a low initial WFNS grade showed deterioration during or following CTA. The neurological condition of the remaining patients with initially high grades did not improve after resuscitation.

Aneurysms could be clearly identified by CTA in all patients. Ruptured aneurysms were located on the bifurcation of the middle cerebral artery in 3 patients, the anterior communicating artery in 1, the anterior cerebral artery in 1, the posterior communicating artery in 1, the supraclinoid internal carotid artery in 1, the basilar tip in 1, and the posterior cerebral artery in 1 (Table 1). The CTA examination apparently demonstrated extravasation of contrast media in 8 patients. The sites of extravasation were all located adjacent to the ruptured aneurysm and confirmed by neuroradiologists. Extravasation was equivocal in 1 patient (Case 4); the presence of contrast leakage was confirmed on DSA.

Surgically Treated Cases: Timing and Outcome

Five of the 9 patients proceeded to surgery immediately (less than 1 hour) after diagnosis of active contrast extravasation during CTA. Three of them (Cases 1–3) underwent decompressive craniectomy and aneurysm obliteration. All of these patients survived with favorable outcomes, and they all had a low WFNS grade on admission. The remaining 2 patients received frontal external ventricular drainage alone (Cases 6 and 7). Both of these patients had a high WFNS grade initially, and their outcomes were poor following immediate surgery.

Delayed surgery (4 hours after CTA) was performed in 1 patient (Case 4). The CTA examination revealed an equivocal finding of contrast extravasation in this case, but subsequent DSA confirmed the presence of extravasation. Aneurysm clipping was performed after angiography, but the patient died 3 days following the operation.

Conservatively Treated Cases

The remaining 3 patients (Cases 5, 8, and 9) did not receive surgical interventions after diagnosis of reruptured aneurysm during CTA. Only 1 of them (Case 5), had a low WFNS grade at presentation, but all 3 patients died within a few days.

Overall Results

The clinical outcomes of reruptured aneurysms during CTA were rated as good outcome in 3 cases (Cases 1–3) and severe disability in 1 (Case 6). Five patients died (Cases 4, 5, 7, 8, and 9). Of those who had a favorable outcome (Cases 1–3), they all manifested with a low WFNS grade at presentation and also received immediate decompressive craniectomy within 1 hour following CTA.

Illustrative Cases

Case 1

This 50-year-old woman presented to our hospital with abrupt headache and in a drowsy state. Based on the neurological examination performed at presentation, her condition was classified as WFNS Grade II. The initial CT examination revealed SAH (Fisher Grade 3) (Fig. 1A), and subsequent CTA showed an aneurysm on the anterior communicating artery (Fig. 1B). An irregular hyperdense infiltration was also found near the aneurysm. Acute contrast extravasation was suspected. At the end of the CTA examination, the patient was found to be in a deep coma (WFNS Grade V). We repeated CT scanning immediately after the CTA series. An enlarged hyperdense lesion was noted near the aneurysm, indicating contrast retained in the extravascular space (Fig. 1C and D). The patient was taken immediately to the operating theater. A large decompressive craniectomy was performed, and the aneurysm was clipped. The patient regained consciousness after the operation and was discharged 3 weeks later. She had minimal disability, an mRS score of 2, and a GOS score of 4 at 12 months after the event.

Case 2

This 34-year-old woman presented to our hospital with disturbance of consciousness after a sudden-onset headache. On the basis of the initial neurological examination, her condition was classified as WFNS Grade II. The initial CT study showed an SAH at the left sylvian fissure (Fisher Grade 4) (Fig. 2A and B). Subsequent CTA showed a saccular aneurysm at the bifurcation of the left middle cerebral artery (Fig. 2C). An irregular hyperdense area, suggesting extravasation of contrast medium, was also found near the aneurysm (Fig. 2C). After the examination, the patient was found to be in a deep coma (WFNS Grade V). We brought her immediately to the operating theater from the CT suite and performed a large decompressive craniectomy within 1 hour after the examination. The aneurysm was clipped simultaneously after hematoma evacuation (Fig. 2D). The patient recovered consciousness after the operation and was discharged to a rehabilitation center. She had only minor disability 12...
Hyperacute aneurysm rerupture

Discussion

Extravasation During CTA

Among patients with nontraumatic SAH, rebleeding following a ruptured aneurysm is a major cause of severe disability and death. Patients with rebleeding during imaging represent a distinct group, characterized by active extravasation of contrast medium. This devastating event is well documented in the era of DSA, and its prognosis is generally poor, with a mortality rate near 80%.10,11 During the early period of SAH (3 hours following the ictus), the incidence of aneurysm rebleeding during CTA is lower than the incidence of rebleeding during DSA. In our series of 9 cases, CTA was always performed within 3 hours of the ictus. Rebleeding of aneurysms during CTA in this hyperacute stage occurred in 14.5% of cases. The reported incidence of active bleeding in CTA varies from 3.3% to 19.7%.4,15 These rates are similar to ours but are much lower than the overall rebleeding rate of ruptured aneurysms within 3 hours of the ictus, which is reportedly 36%.21 This indicates that CTA probably does not cause aneurysm rebleeding.4,15 In contrast, in patients undergoing DSA within 3 hours of the ictus, the reported rate for aneurysm rebleeding during the examination is 23.9%.12 This higher incidence in comparison with that during CTA may be explained by the duration of the study as well as the induction of rebleeding by intraarterial contrast injection.15,19 Therefore, it is believed that CTA is a time-saving and less complicated alternative in the acute phase of SAH and probably does not cause aneurysm rebleeding.2,4

Aneurysm Rerupture During CTA: a Potentially Lethal Condition

Detection of extravasation during CTA is an indicator of a poor prognosis.4,15,18 In the acute stage of SAH, most patients with reruptured aneurysms during CTA

months after the event, with an mRS score of 2 and a GOS score of 4.

Table 1: Characteristics of patients with aneurysm rerupture during CTA

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Aneurysm Location</th>
<th>Time Btwn Ictus &amp; CTA</th>
<th>WFNS Grade At Presentation</th>
<th>Time Btwn CTA &amp; Surgery/TAE</th>
<th>Procedure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holodny et al., 2003</td>
<td>35, M SHA</td>
<td>&gt;7 days</td>
<td>I I or II</td>
<td>&gt;1 hr</td>
<td>clipping</td>
<td>good</td>
<td></td>
</tr>
<tr>
<td>Kusumi et al., 2005</td>
<td>45, M ACoA</td>
<td>1 hr</td>
<td>V V</td>
<td>12 hrs</td>
<td>TAE</td>
<td>death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59, M MCA</td>
<td>&lt;2 hrs</td>
<td>V V</td>
<td>no surgery/TAE</td>
<td></td>
<td>death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>71, M MCA</td>
<td>&lt;3 hrs</td>
<td>V V</td>
<td>5 hrs</td>
<td>TAE, hematoma evacuation</td>
<td>death</td>
<td></td>
</tr>
<tr>
<td>Hashiguchi et al., 2007</td>
<td>79, F PCA</td>
<td>&lt;3 hrs</td>
<td>V V</td>
<td>no surgery/TAE</td>
<td></td>
<td>death</td>
<td></td>
</tr>
<tr>
<td>Josephson et al., 2004</td>
<td>71, F ICA</td>
<td>&lt;3 hrs</td>
<td>V V</td>
<td>no surgery/TAE</td>
<td></td>
<td>death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41, F BA</td>
<td>&lt;3 hrs</td>
<td>V V</td>
<td>no surgery/TAE</td>
<td></td>
<td>death</td>
<td></td>
</tr>
<tr>
<td>Pérez-Núñez et al., 2006</td>
<td>45, F ICA bifurcation</td>
<td>&lt;2 hrs</td>
<td>V V</td>
<td>immediate EVD</td>
<td>vegetative state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Im et al., 2007</td>
<td>68, M ACoA</td>
<td>30 mins</td>
<td>NR NR</td>
<td>no surgery/TAE</td>
<td></td>
<td>death</td>
<td></td>
</tr>
<tr>
<td>Nakada et al., 2000</td>
<td>55, M ACoA</td>
<td>NR NR</td>
<td>NR NR</td>
<td>no surgery/TAE</td>
<td></td>
<td>death</td>
<td></td>
</tr>
<tr>
<td>Ryu et al., 2005</td>
<td>55, M ACoA</td>
<td>&gt;1 day</td>
<td>NR NR</td>
<td>24 hrs</td>
<td>good</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>42, M pericallosal</td>
<td>NR NR</td>
<td>NR NR</td>
<td>immediate</td>
<td>EVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>present study (case no.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50, F ACoA</td>
<td>1 hr</td>
<td>II V</td>
<td>immediate</td>
<td>large craniectomy &amp; clipping</td>
<td>good</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>34, F MCA</td>
<td>1 hr</td>
<td>II V</td>
<td>immediate</td>
<td>large craniectomy &amp; clipping</td>
<td>good</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>65, F MCA</td>
<td>0.5 hr</td>
<td>II V</td>
<td>immediate</td>
<td>small craniectomy &amp; clipping, extended craniectomy on 3rd day after clipping</td>
<td>good</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>55, M ICA</td>
<td>1 hr</td>
<td>II IV</td>
<td>4–5 hrs</td>
<td>clipping</td>
<td>death</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>81, F BA</td>
<td>1.5 hrs</td>
<td>II IV</td>
<td>no surgery/TAE</td>
<td></td>
<td>death</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>82, F MCA</td>
<td>2 hrs</td>
<td>IV V</td>
<td>immediate</td>
<td>EVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>34, F PCA</td>
<td>&lt;2 hrs</td>
<td>IV V</td>
<td>immediate</td>
<td>EVD</td>
<td>death</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>85, F PCoA</td>
<td>1 hr</td>
<td>IV V</td>
<td>no surgery</td>
<td></td>
<td>death</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>43, F ACA</td>
<td>1 hr</td>
<td>V V</td>
<td>no surgery</td>
<td></td>
<td>death</td>
<td></td>
</tr>
</tbody>
</table>

* ACoA = anterior communicating artery; BA = basilar artery; EVD = external ventricular drainage; ICA = internal carotid artery; MCA = middle cerebral artery; NR = not reported; PCA = posterior cerebral artery; PCoA = posterior communicating artery; SHA = superior hypophyseal artery; TAE = transarterial embolization.
have a poor neurological condition at presentation. For those who present with good condition, deterioration in the acute stage is still possible. In our series, 44.4% of patients (4 of 9) had a high WFNS grade at presentation; the grade remained poor throughout the course of the study. The rest of the patients had a low WFNS grade initially, but their condition deteriorated rapidly during or immediately after CTA. Overall, poor outcome occurred in 66.7% of patients. Nakatsuka et al.15 reported on 3 patients who had extravasation on CTA. All of these patients were admitted with low Glasgow Coma Scale scores, and they all died despite treatment. Hashiguchi et al.,4 who reviewed previously reported cases, also found that the majority of patients who suffered active bleeding from aneurysms had a very poor outcome. This turns active contrast extravasation during CTA into an adverse prognostic factor for patients with ruptured aneurysms.

Surgery in the Hyperacute Stage

Despite a very poor clinical outcome reported in the literature, in our experience, effective treatment remains possible following rebleeding in CTA. In the literature, we found 12 reported cases of aneurysm rupture during CTA. We gathered data from all of these cases and analyzed their outcomes, together with those of our own series, according to several prognostic factors.

For patients with initially high WFNS grades (Cases 6–9 and 11–17), the outcomes remained poor with or without aggressive treatment (Fig. 3). These results concurred with those of Hutchinson et al.,6 who observed that poor-grade SAH patients who remained unresponsive following resuscitation had an overall poor outcome. Therefore, active and aggressive treatments were not advised for these patients.

In contrast, selected patients with good neurological presentations can make a favorable recovery. All except 1 of the 6 patients who had a low WFNS grade showed rapid deterioration, corresponding to a rate of 83% (Fig. 3). The patient without neurological deterioration during CTA (whose case was reported by Holodny et al.2) showed good recovery after a delayed surgery. Of the remaining 5 patients with neurological deterioration, 3 underwent immediate operation after the diagnosis of active extravasation (Cases 1–3). Two of these, who underwent large decompressive craniectomies and aneurysm clipping, survived with favorable outcomes (Cases 1 and 2). The remaining patient (Case 3) received a small craniectomy and insufficient hematoma evacuation. She regained consciousness on the 2nd day after the operation, but her intracranial pressure gradually increased, causing an unsatisfactory immediate recovery after another emergency operation. She underwent an extended craniectomy on the 3rd day after the first operation. She regained consciousness gradually and had a favorable outcome at the
Hyperacute aneurysm rerupture

3-month follow-up evaluation. In contrast, patients who did not receive immediate surgical treatment following the diagnosis of active bleeding died within a few days (Cases 4 and 5).

Because a large craniectomy can efficiently prevent uncal herniation in the presence of severe post-SAH brain edema, Smith et al. have proposed that this procedure can be successfully applied in poor-grade SAH patients presenting with large sylvian hematomas. They observed that the posterior margin of a large decompressive craniectomy should reach 2 cm behind the external auditory meatus. The craniectomy extended this far in Cases 1 and 2 in our series. In Case 3, however, the craniectomy window was quite narrow, and its posterior margin did not extend past the external auditory meatus; this probably explained the patient’s unsatisfactory recovery after the first operation even though the surgery was performed in the hyperacute stage.

Although no statistical analysis can be performed in this small group of patients, our findings indicate that favorable outcomes can indeed be achieved in a selected group. This policy does not increase the rate of poor outcomes, including vegetative states and severe disabilities, if an appropriate treatment strategy is chosen. Favorable outcomes appear to be associated with low initial WFNS grade, stable neurological condition during CTA, and immediate operation in the setting of neurological deterioration. Additionally, the surgical procedure should efficiently relieve intracranial hypertension after severe SAH. Thus, we suggest that emergent decompressive craniectomy and aneurysm clipping could benefit patients with good neurological status at presentation and should not be delayed in the presence of rapid neurological deterioration when CTA shows contrast extravasation.

Conclusions
Contrast extravasation during CTA will be an in-
creasingly common phenomenon as CTA is more widely used for the initial evaluation of spontaneous SAH. Although these cases have generally been considered hopeless, we have attempted to identify a clinical subgroup that may benefit from surgery in the hyperacute stage. Clinical condition at presentation, the interval from ictus to CTA, and the interval from ictus to operation must be critically considered. We propose that in the presence of active bleeding during CTA, early surgical decompression should be performed in patients who had good initial neurological status with rapid neurological deterioration during CTA, but not in patients classified as poor grade at initial presentation.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following: Conception and design: Wang. Acquisition of data: Su, Chen. Analysis and interpretation of data: Tsuang. Drafting the article: Tsuang, Su. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Wang. Statistical analysis: Lee. Administrative/technical/material support: Chen, Lai, Tu.

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