

# Thrombolysis in Acute Ischemic Stroke at a Rural Tertiary Hospital: A Case Series of the First 50 Patients (2016–2021)

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## ABSTRACT

**Objectives.** To determine the outcomes for patients with acute stroke improve with early intervention in a series of the first 50 patients with acute ischemic stroke who were thrombolysed at our center.

**Methods.** National Institutes of Health Stroke Scale (NIHSS) scores were recorded by NIHSS-certified nurses-on-duty in their appropriate monitoring sheets in the chart, which was double-checked by the neurology consultant co-author on duty. Source chart entries were cross-checked with logs from the CT scan, pharmacy, and other department records before being collated by the primary author. Means and averages were used to describe the patients' data.

**Results.** We included the first 50 patients with acute ischemic stroke, eligible for and who consented for thrombolysis. The patients had an average age of 61 years (range: 29 to 87); 32 (64%) were  $\geq 60$  years; 16 (32%) were male. Male gender (24/50), age  $\geq 60$  years old (32/50), hypertension (30/50), heart disease (6/30), smoking (7/30), and ethanol intake (9/30) were the most common risk factors. Thirty-five (70%) suffered a moderate stroke. The mean NIHSS of the 50 patients was 12.6 (range: 2 to 28). All but one received intravenous recombinant tissue plasminogen activator (IV rTPA) within 4.5 hours of onset, at a dose of 0.6 to 0.9 mg/kg. Symptomatic hemorrhagic transformation occurred in one (2%); asymptomatic hemorrhagic transformation was seen in three (6%). Fifteen of the 50 (30%) were NIHSS = 0 on discharge; another 18 (36%) showed clinical improvement compared to their status upon admission. Three patients (6%) were mRS = 0; and 30 (60%) were at least ambulatory (mRS  $\leq 3$ ) on discharge. Four patients (8%) died, one (2%) from fatal hemorrhagic transformation. Ten patients (20%) developed nosocomial pneumonia; two (4%) had catheter-related urinary tract infections. More than half (52%) did not develop any in-hospital complications. The patients were admitted for a mean of 6.6 days (range < 24 hours to 20 days). The average gross bill was ₱56,041.34 (range: ₱8,729.83 to ₱182,054.08); ₱32,194 was the average amount our Center shouldered per patient (range: zero to ₱154,272.88); almost all were Charity Service patients who used the ₱19,600 Philippine Health Insurance Corporation case rate and the 20% senior citizen discount to help defray the costs of their hospitalization.

**Conclusion.** Stroke thrombolysis can be done in a rural tertiary hospital safely and effectively if with strong government, administration, health care workers, and community support.

**Keywords:** ischemic stroke, rural hospital, thrombolysis

## INTRODUCTION

Approximately one in every 50 Filipinos suffers a stroke,<sup>1</sup> and 70% of strokes are ischemic in nature.<sup>2</sup> Stroke and other vascular diseases rank 2<sup>nd</sup> in the leading causes of death in the Philippines,<sup>1,3</sup> and one out of three stroke patients are permanently disabled.<sup>4</sup> A stroke is a brain attack; it is an emergency but is treatable and preventable.<sup>4</sup> Almost two

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million neurons are lost per minute in an acute ischemic stroke, without treatment.<sup>5</sup>

In 2016, intravenous recombinant tissue plasminogen activator (IV rTPA) was made available by the Department of Health (DOH) for free to all hospitals capable of treating acute ischemic stroke through the Stroke Medicines Access Program (SMAP); our center was one of its access points.<sup>6</sup>

Our center is a DOH-retained apex hospital in Region I, with more than a thousand employees, receiving referrals from northern Ilocos Sur, Ilocos Norte, northern Cagayan, and northern Cordillera Autonomous Region (CAR) – roughly 3,000,000 in population.<sup>7</sup> It is one of two stroke-ready hospitals identified by the Stroke Society of the Philippines in Ilocos Norte in 2018.<sup>8</sup> In 2016, there were 427 stroke admissions at our center; by 2020, even during the COVID-19 pandemic, our stroke admissions reached 724 in a year.<sup>9</sup> At the onset of the SMAP, our center did not yet have its computed tomogram scanning (CT scan) machine. Thus, to execute the program, we had partnerships with nearby private centers with their own CT scans for expeditious CT scanning of patients with acute stroke. Our center has since acquired its own in-house CT scanner; however, with our center's expansion, the laboratory is now at a greater physical distance from the emergency room than when the SMAP started. After the SMAP ended, our center continued intravenous thrombolysis even after the loss of free IV rTPA. We present here our first 50 cases.

## OBJECTIVES

### General Objective

To describe our series of patients with acute ischemic stroke thrombolysed with IV rTPA

### Specific Objectives

To describe the:

1. Demographic profile
2. Admission characteristics
3. Stroke severity by:
  - a. National Institutes of Health Stroke Scale (NIHSS) score; or, by
  - b. Stroke Society of the Philippines (SSP) severity category
4. rTPA dose given
5. Outcomes:
  - a. mortality rate
  - b. NIHSS at discharge
  - c. modified Rankin Scale (mRS) score at discharge
6. Complications
  - a. hemorrhagic complication rate
  - b. nosocomial infection rate
7. costs of care
  - a. length of stay
  - b. gross hospital bill
 of our patients treated with rTPA.

## MATERIALS AND METHODS

### Sampling Strategy

We used total enumeration of 50 patients who received IV rTPA infusion in this series. All 50 patients were referred to at least one of the neurologist co-authors during their admission.

### Ethical Issues on Human Subjects

Approval by the Research Ethics Review Committee (RERC) was sought before the retrieval and review of the first 12 cases at the start of the series, to expand the chart review period in the succeeding years, and to submit this paper for final publication. Patient identifiers were removed or kept confidential; charts were accessed through the Health Information Management System (HIMS) with appropriate permissions.

### Outcome Measures

#### 1. Stroke Severity

Stroke severity was described using the patient's NIHSS score on admission; or, the stroke severity descriptors by the SSP:<sup>4</sup>

- a. Mild: NIHSS 1 to 5; or, alert patient with any (or a combination) of the following: pure motor weakness on one side of the body, can raise arm above the shoulder, has clumsy hand, or can ambulate without assistance; pure sensory deficit; slurred but intelligible speech; vertigo with incoordination, gait disturbance, unsteadiness; visual defects;
- b. Moderate: NIHSS 6 to 21; or, awake patient with significant motor and/or sensory and/or language and/or visual deficit(s); or, disoriented, drowsy, or light stupor with purposeful response to painful stimuli;
- c. Severe: NIHSS > 21; or, deeply stuporous or comatose patient with non-purposeful responses, decorticate posturing, or decerebrate posturing to painful stimuli; or, comatose patient with no response to painful stimuli.

NIHSS scores were recorded by the NIHSS-certified stroke nurses on duty and recorded in their appropriate monitoring sheets in the chart. The primary author encoded and deidentified the data in the final manuscript.

#### 2. Modified Rankin Scale score questionnaire by Bruno et al.<sup>10</sup>

##### mRS 0:

Q: Are you completely back to the way you were right before your stroke?

A: Yes.

**mRS 1:**

Q1: Can you do everything that you were doing right before your stroke, even if slower and not as much?

A1: Yes.

Q2: Are you completely back to the way you were right before your stroke?

A2: No.

**mRS 2:**

Q: Can you do everything that you were doing right before your stroke, even if slower and not as much?

A: Yes.

**mRS 3:**

Q1: Could you live alone without any help from another person? This means being able to bathe, use the toilet, shop, prepare or get meals, and manage finances?

A1: No.

Q2: Can you walk from one room to another without help from another person?

A2: Yes.

**mRS 4:**

Q1: Can you walk from one room to another without help from another person?

A1: No.

Q2: Can you sit up in bed without any help?

A2: Yes.

**mRS 5:**

Q: Can you sit up in bed without any help?

A: No.

**Data Collection Instruments and Technologies**

Data was collected and tabulated using Microsoft Excel and Apple Pages. After the spreadsheets were printed and collated, one copy was retained by the authors, one copy was submitted to the RERC, and the rest were deleted.

**Data Processing**

The names of the patients who received IV rTPA were retrieved from the Pharmacy census, and their charts were retrieved from the HIMS. The patients' full names were not recorded in the spreadsheets, only their initials and case numbers; these were excluded from the final manuscript.

**Data Analysis**

Measures of central tendency were used to describe the patients' general age, gender, NIHSS scores, and other parameters.

**Techniques to Enhance Trustworthiness**

Source chart entries were checked by the neurologist co-authors during patient rounds and nurse supervisor co-author during duty rounds. This data was cross-checked with logs from the CT scan and Pharmacy departments before being collated by the primary author.

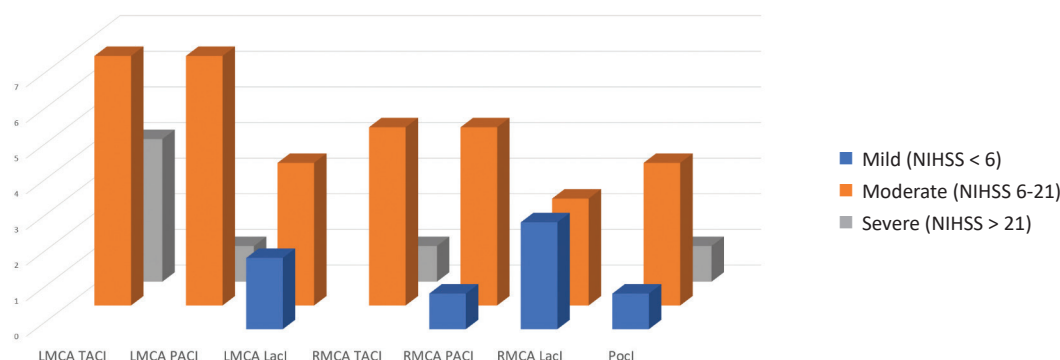
**RESULTS**

We administered rTPA to 50 patients from September 2016 to March 2021 and retrieved their records for this series. Approximately 1.4% of the total stroke admissions per year were thrombolysed.

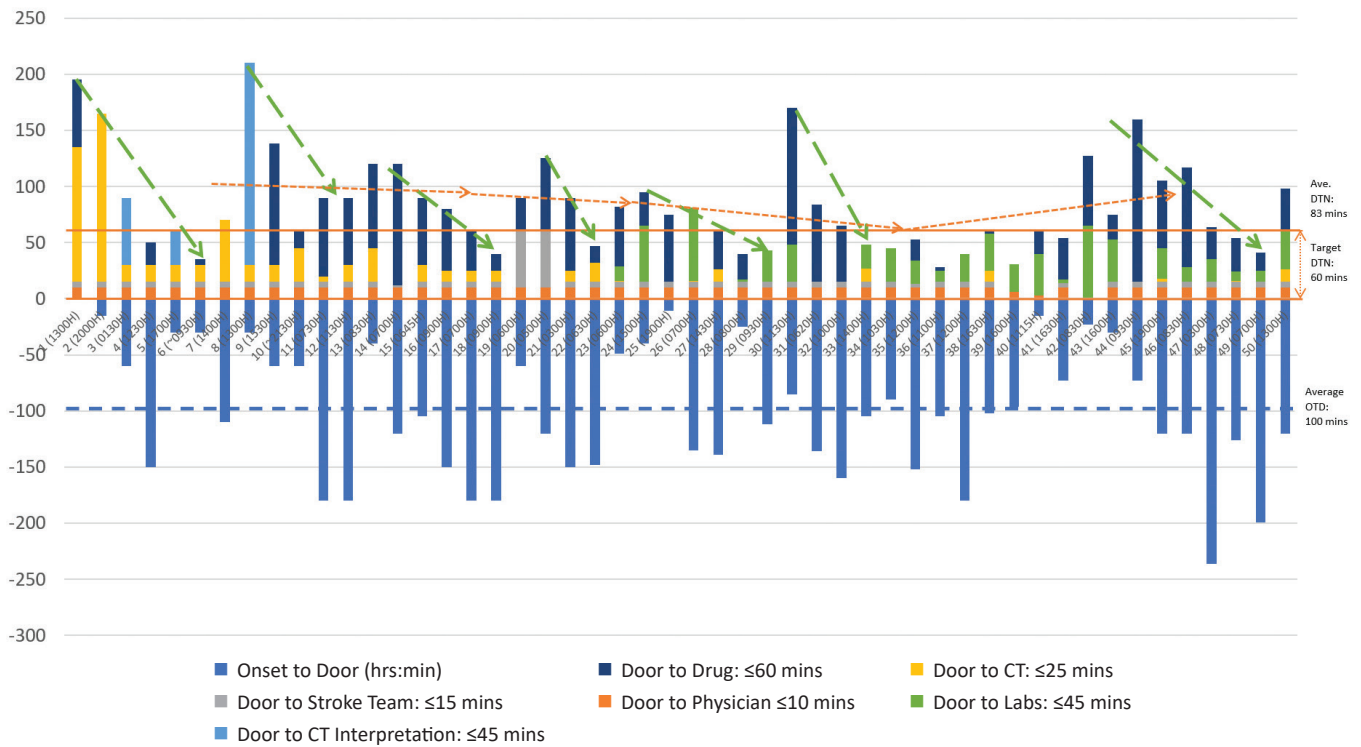
The patients had an average age of 61 years (range: 29 to 87); 32 (64%) were ≥ 60 years old; 24 (48%) were male. Advancing age (32/50 patients, 64%) was the most common non-modifiable stroke risk factor. Hypertension (30/50, 60%), ethanol intake (9/50, 18%), and heart diseases (8/50, 16%) were the most common modifiable risk factors. All were non-ambulatory (i.e., modified Rankin Scale ≥ 4) upon admission.

Ten patients were referred from a secondary hospital with a CT scan, or underwent ambulance conduction for outside CT scanning; the rest underwent CT scanning and subsequent rTPA infusion all at our center.

Thirty-five of the 50 patients (70%) suffered a moderate stroke with a mean NIHSS score of 12.6 (range: 2 to 28). About half had a left anterior circulation infarct (Figure 1).



**Figure 1. Stroke syndrome and stroke severity on admission.** LMCA, left middle cerebral artery; RMCA, right middle cerebral artery; TACI, total anterior circulation infarction; PACI, partial anterior circulation infarction; PoCI, posterior circulation infarction.



**Figure 2. Onset-to-door (OTD), and door-to-needle (DTN) times.** Each stacked bar shows the time points for each patient. The time of emergency room arrival was set as Minute Zero. The dark blue bars show each patient’s stroke onset-to-door time. The emergency room team-on-duty includes the Internal Medicine physician-on-duty, who is also a member of the Stroke Team, accounting for the short orange bars. Patients 1, 2, and seven were conducted to an outside CT scanner, accounting for their notably long door-to-CT times shown in yellow bars. The CT was not immediately interpreted in patient 8 (light blue bar). Starting from patient 23, door-to-labs times increased (shown in light green bars), because the laboratory moved to a more distant building separate from the emergency room. The navy-blue peaks in the door-to-drug times account for the shifting-in of the new emergency room Internal Medicine physicians-on-duty, and the peaks decreased with time as physicians gained experience and confidence (green dashed arrows). The average door-to-needle time per year gradually decreased over the first four years, before increasing again in the fifth year during the COVID-19 pandemic (orange dotted arrows).

Almost half presented in the morning between 0600H and 1200H. On average, the patients received IV rTPA at 83 minutes from stroke onset, from a high of 104 minutes in our first year to just over 60 minutes before the COVID-19 pandemic. All but one patient were given rTPA under 4.5 hours, after ruling out relative contraindications to giving the drug at this extended time window. The patients received a dose between 0.6–0.9 mg/kg of rTPA (mean 0.618 mg/kg). All patients were admitted to the Neuro/Coronary Care Unit (or to its COVID-19 holding area) for close monitoring (Figure 2).

Fifteen patients (30%) were discharged with an NIHSS score of zero; 18 (36%) clinically improved to a milder stroke severity category; 12 (24%) remained in the same stroke severity category; one (2%) clinically worsened after hemorrhagic conversion. Four patients (8%) succumbed: to hemorrhagic conversion, non-ST elevation myocardial infarction, sepsis from nosocomial pneumonia, and sudden cardiac death, respectively (Figure 3).

Nine (18%) developed hemorrhagic complications. Four (8%) developed parenchymal hemorrhagic conversions; two (4%) of these were symptomatic hemorrhagic conversions, one (2%) of these was fatal; the other two (4%) hemorrhagic conversions were asymptomatic.

Five (10%) developed milder bleeding complications; two (4%) with upper gastrointestinal bleeding; and one (2%) each with gum bleeding, hematuria, and soft tissue hematoma in the calf, respectively.

Ten patients (20%) developed nosocomial pneumonia; two (4%) had catheter-related urinary tract infections. More than half (26 of 50, 52%) did not develop any in-hospital complications (Figure 4).

The modified Rankin Scale score was not definitively recorded and was inferred from the doctor’s and/or nurses notes, in 12 of the 50 cases.

Following this, patients who were described as “stretcher-borne” or “wheelchair-borne” in the doctors’ and/or nurses’ notes were inferred to be at least mRS 4; those

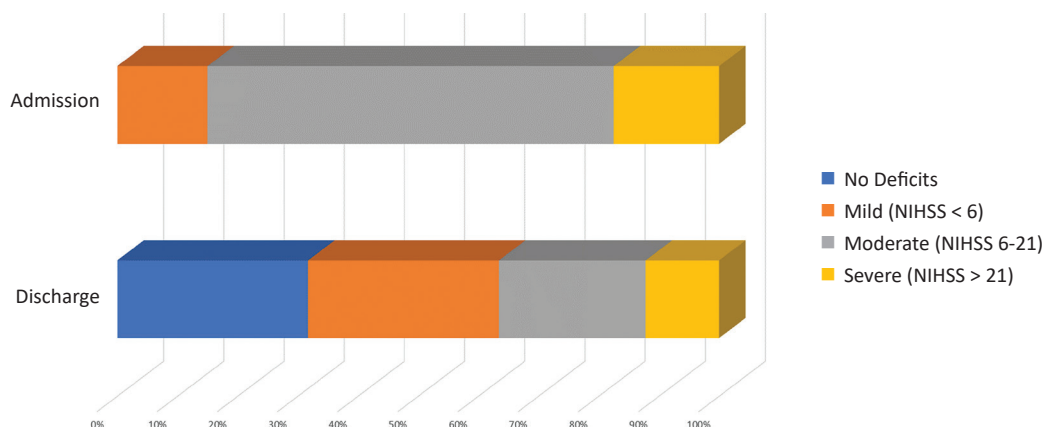


Figure 3. Admission and discharge National Institutes of Health Stroke Scale Scores.



Figure 4. 😊 no deficits, no hemorrhagic complications; 😊 no deficits, but with hemorrhagic complications; 😊 improved deficits, no hemorrhagic complications; 😊 improved deficits, but with hemorrhagic complications; 😊 stable deficits, no hemorrhagic complications; 😊 stable deficits, but with hemorrhagic complications; 😞 worse deficits, with hemorrhagic complications; 🌸 died; non-neurologic cause of death; 🌸 died; neurologic cause of death.

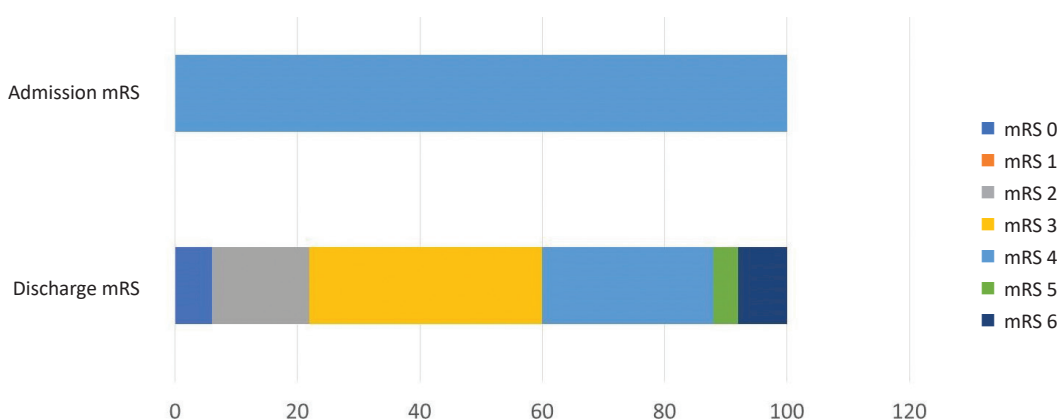


Figure 5. Admission vs discharge Modified Rankin Scale (mRS) score.

\*mRS Scores were inferred in 12 of the 50 cases.

described as “ambulatory” were inferred to be at least mRS 3; those described as “feeding self-unassisted” or “consumed prepared hospital food by him/herself” were inferred to be at least mRS 2. Acknowledging this limitation, we report that three patients (6%) were discharged mRS 0, four patients (8%) were mRS 2, four patients (4%) were at least mRS 2, 14 patients (28%) were mRS 3, five patients (10%) were at least mRS 3, 12 patients (24%) were mRS 4, two patients

(4%) were at least mRS 4, one patient (2%) was mRS 5, one patient (2%) was at least mRS 5, and four patients (8%) died, i.e., mRS 6 (Figure 5).

The patients were admitted for a mean of 6.6 days (range < 24 hours to 20 days). The average gross bill was ₱56,041.34 (range: ₱8,729.83 to ₱182,054.08). Almost all were Charity Service patients. In compliance with the ‘No Balance Billing policy’,<sup>11</sup> our center shouldered the excess



not covered by the 20% senior citizen discount on the gross bill, and the ₱19,600 Philippine Health Insurance Corporation case rate<sup>12</sup> on the net bill (35% to 44% of the average gross bill, depending on the patient's age), with no additional out-of-pocket expenses for these Charity Service patients. The mean hospital share was ₱32,194 per patient (range: zero to ₱154,272.88); our center provided about ₱1,255,563.72 over five years to support the hospitalization of these 50 patients.

## DISCUSSION

Our series shows that, at a tertiary rural hospital, with time, staff training, and administrative support, acute ischemic strokes can be thrombolysed with intravenous recombinant tissue plasminogen activator within recommended time windows and with favorable clinical outcomes.

More than ten years ago, a stroke awareness gap was identified, in that about a third of the general population does not know what a stroke is, or what to do if a person has a stroke.<sup>13</sup> Our onset-to-door time of 100 minutes shows that there is still room for improvement for public health information campaigns and programs to close this gap.

Previously, patients were conducted to an outside laboratory for emergency cranial imaging and thrombolysis, before returning to our center for post-infusion monitoring, until our center acquired its own CT scanner and the whole Brain Attack pathway could be completed in-house. However, our door-to-laboratory time increased ever since our laboratory moved to a new, geographically distant building from our emergency room; a satellite laboratory is being planned to be set up in our new emergency room, capable of stat complete blood count and other basic emergency laboratory tests.

We were also able to document the "learning curve" of our new incoming emergency room physicians, and how their door-to-needle times would decrease with time and experience, underlining the need for continuous staff training and education in stroke care.

Our average door-to-needle time had been decreasing near to the target of 60 minutes until the COVID-19 pandemic upended our systems of care. In one United States study, COVID-19 was observed to lower the odds of rTPA infusion within 60 minutes by 45%.<sup>14</sup> Patients should not stay at home if they suffer a stroke, despite the ongoing COVID-19 pandemic; however, the limitation of traffic movements, COVID-19 triaging, donning and doffing of personal protective equipment, and other added health protocols erased the progressive time gains we made over the years.

Our NIHSS outcomes on discharge are similar to the classic NINDS TPA trial, in that, approximately two-thirds have no-to-minimal deficits.<sup>15</sup> Our in-hospital mortality rate is lower than that reported in local data (8% vs 14.6%). Our asymptomatic hemorrhagic transformation

rate was also lower at 4% (two of the 50), compared to 24.8%. Symptomatic hemorrhagic transformation was seen in one (2%, versus 12.1%).<sup>16</sup> Compared to a similar hospital-based series from Vietnam, their thrombolysis rate was better (2%, vs our ~1.4%) and their mortality rate was lower (2.1% vs our 4%); but our symptomatic intracranial hemorrhage rates were comparable (5/121, vs our 2/50) using a comparable average dose of 0.62 mg/kg of rTPA.<sup>17</sup>

At present, our center is now more organized as a hub-and-spoke model of community stroke care.<sup>4</sup> The challenges now are to continue to increase stroke awareness in the community; to share our technical knowledge and skills to our neighboring hospitals for them to be able to raise their level of stroke care as well; to encourage our referring partners to endorse and transfer their patients more expeditiously; to maintain our services and technical skills in the face of staff rotating or leaving; to acquire and to adjust to our new infrastructure; to continue to provide free rTPA even after the SMAP has ended; and, to adapt again to this new milieu with COVID-19 in the community.

When the DOH still provided free rTPA to SMAP access points like our Center, our hospital's share in the patient's bill was zero, with the total costs of care covered by the Philippine Health Insurance Corporation's case rate. We are thankful for our hospital administration's decision to absorb the excess costs incurred per patient after the SMAP ended, and allow us to continue to provide IV rTPA to our catchment area, recognizing that not all hospitals in our locality have the resources to start or continue this service. As of this writing, our center remains the most active in providing intravenous thrombolysis in our area.

Our reported data was limited by retrievable physical and digital chart records. The lack of data for the patients without explicitly recorded discharge modified Rankin scores highlighted the need for better documentation of our post-stroke outcomes. We also need to identify points for improvement in our post-stroke rehabilitation care, where mRS 3 and mRS 2 are separated by the ability of the patients to perform activities of daily living. Smoking and alcoholism or ethanol intake, were described qualitatively, as with or without smoking or ethanol intake, respectively. Times were estimated to the nearest minute, as the clocks were not synchronized down to the second.

## CONCLUSION AND RECOMMENDATIONS

With a paucity of data on stroke thrombolysis in the Philippine rural setting, this paper shows that thrombolysis can be done anywhere with strong support from the government, hospital administration, medical community, and public.

This paper also shows that data collection and reporting on the status of stroke care in the country needs to increase and to improve.

With the growth of the Department of Physical Medicine and Rehabilitation in our center, another paper following the post-discharge recovery of our patients undergoing psychiatric care despite the COVID-19 pandemic should be made. Further studies to explore how different operational strategies mitigated the negative effects of the COVID-19 pandemic on our health systems should also be done.

### Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis data, drafting and revising and approved the final version submitted.

### Author Disclosure

All authors declared no conflicts of interest.

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