GEOSPATIAL AND TRANSPORT MODELING IN STROKE SERVICE PLANNING

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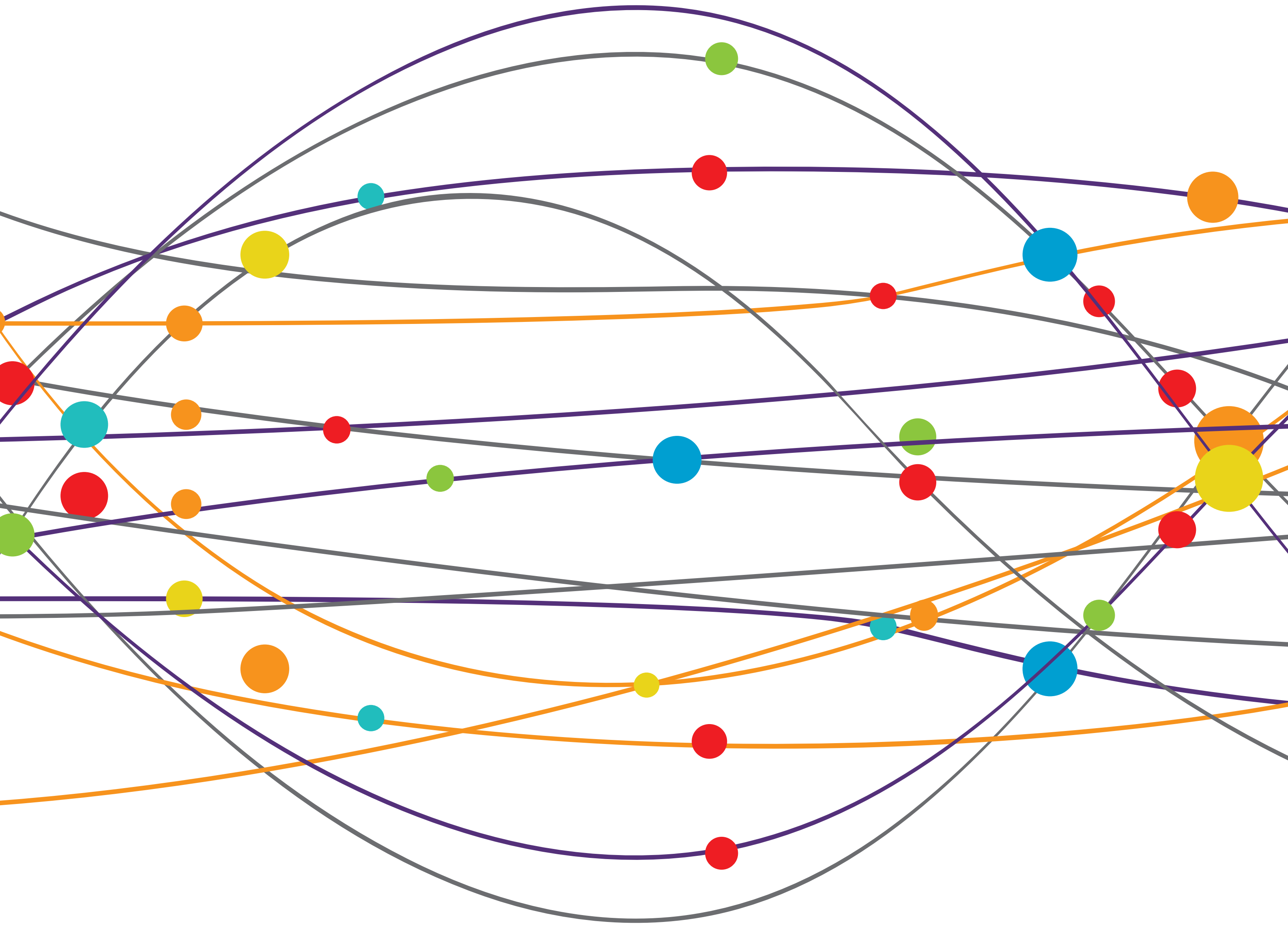

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GEOSPATIAL AND TRANSPORT MODELING IN STROKE SERVICE PLANNING

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EDITORIAL
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Editorial: Geospatial and Transport Modeling in Stroke Service Planning

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Keywords: geospatial, transport, model, access, stroke

Editorial on the Research Topic

Geospatial and Transport Modeling in Stroke Service Planning

Recent advances in acute stroke therapy, endovascular clot retrieval, and clot busting drugs (1, 2), have re-focused emphasis on appropriate and timely transportation of patients for treatment. The implementations of these medical breakthroughs are equally as important as the clinical trials and are critical to translation of these trial findings. The implementation phase requires support in terms of government policy (Allen et al.; Mathur et al.), pre-hospital (Holodinsky et al.; Phan et al.; Tajaddini et al.; Vidale et al.), and hospital cares (Seah et al.). At all stages, one needs to develop models with fair access for all patients to the best stroke therapy whether they live in metropolitan or remote areas (Mathur et al.). These desires need to be balanced by the limited workforce of neurologists with interest in stroke or stroke physicians.

Complementing these advances, exploration of ideas in operational research can help the balancing act in determining appropriate hospitals for transport given the degree of stroke severity for that patient. In this special issue, investigators had created a web based apps to allow clinicians to estimate the impact of various additions (e.g., adding CT Perfusion or Telemedicine) to mobile stroke unit (MSU) on the operating range of MSU (Phan et al.). These investigators found that the range of MSU can be extended to 76 min from base. On the other hand, addition of CT Perfusion and Telemedicine would reduce the operating range of MSU. Investigators next explored the location of MSU in a metropolitan city (Phan et al.). This study reveals that some inner city suburbs are well-serviced and within 30 min of up to 10 hospitals. One may surmise that the deployment of MSU in these over serviced suburbs may not be fair. Perhaps MSU should be deployed in the peripheral suburbs that are less well-served by hospitals providing either endovascular clot retrieval (ECR) or clot busting therapy (Phan et al.). In the exploration of the location for clot retrieval hubs, investigators found several different combinations of hospital which can serve a metropolitan city as Sydney, Australia (Phan et al.). The investigators extended their earlier work with mapping location of clot retrieval service in Melbourne (3), Australia by adding the constraint of expected number of clot retrieval cases. The expected number of cases can be estimated from the census data for each suburb and stroke incidence studies (2). The investigators found that assuming a 3-hospital model and 15% of patients eligible for clot retrieval, the expected number of cases to be handled by each hospital is 465 (∼9 cases per week). This number drops down to 374 if a 4-hospital model is preferred (∼7 cases per week) (Phan et al.).

Remote and sparsely populated areas and low income countries present very different challenges to delivery of emergency stroke services, with limited clinical resources, long travel times, and well-known disparities in many key metrics in comparison to urban populations. Improved care delivery involving MSU, including airborne MSU, is complex (Mathur et al.). Investigators have reviewed

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a range of strategies used by health services internationally when deploying MSU and explored the complex interplay between distribution of health-care resources, expertise, costs, pre-hospital screening, and technological advances, including telemedicine.

Pre-hospital screens are a key component in decision making by emergency services personnel, potentially contributing to the choice of the most appropriate treatment destination for the stroke patient. If, for example, occlusions of large arteries can be detected reliably (Holodinsky et al.; Phan et al.; Tajaddini et al.; Vidale et al.) in pre-hospital screens then patients can be transported directly to emergency clot retrieval centers, bypassing smaller centers and avoiding delays (Lima et al.). The research shows how these screening tools can be combined with technologies and models to assess which hospital the patient should be transported to Holodinsky et al. and Lima et al. Additionally, transport of stroke patients has often been dichotomized as two potential options: Drip and Ship, where the patient is first transported to the *closest* thrombolysis then transferred to the *closest* clot retrieval hospital; and Mothership where the closest stroke hospital is bypassed in favor of the *closest* clot retrieval hospital (Holodinsky et al.). However, a study shows that all potential transport options should be considered (Schlemm et al.).

Improvement in efficiency of communication between clinicians in the extremely complex stroke treatment pathway has the potential to reduce the time to reperfusion of stroke cases. An open source application (Seah et al.), based around secure mobile phone communication and web interfaces and linking management, assessment, and investigation teams is undergoing trials. The application exploits real-time geospatial information to track patients and arrival times of physicians. Investigators intend to make their software freely available. Continuing the theme of open source software underpinning improvements in stroke service delivery is an introduction to open source geospatial analysis tools (Padgham et al.). A tutorial-style introduction to fundamentals of geospatial analysis, in the context of stroke service delivery, is provided. Source code and data are available to support researchers becoming familiar with possibilities offered by the vast range of online data and visualization services and freely available analysis tools.

Mathematical models have also played a critical role in the creation of best pre-hospital transport destination as well the optimization of the location stroke centers. Mathematical algorithms that take into account drive times, hospital efficiencies, and pre-hospital stroke screening tools developed from the decay curves of pooled randomized control trial data have been used to create an online interactive software that shows best transport destination for the patient, and the usability of this software has been assessed (Holodinsky et al.). This software can be used by healthcare administrators to develop pre-hospital transport protocols that define transport boundaries based on hospital performance. Similarly, a multi-object genetic algorithm was developed to optimize the number hyper-acute stroke hospitals in England, which used the following optimization parameters: number of hospitals; travel time; proportion of patients within 30 min; and number of stroke admissions to the hospital (Allen et al.). This study was used to influence policy.

We often assume that ambulance travel time is much faster than that by car. This scenario may not be true (3) as some countries do not allow ambulance traveling with light and sirens to drive the wrong way down the road. This is worrying as the population in metropolitan areas increases with time and timely transport of patients will become a major issue (Tajaddini et al.). We had explored this issue by using strategic transport model and which contains data on proposed road network and future population growth. These models have an advantage over Google Maps application programming interface (API) as this latter technology based the trip time estimate on crowd source data on moving cars and current roads (not proposed roads in the future). A disadvantage of such strategic model is that the road network data used in the modeling process is deemed confidential as some proposed road may or may not be built.

The vision of this Research Topic in the Stroke section of Frontiers in Neurology was to discuss contemporary issues in pre-hospital care, emergency service transport of patients (including mobile stroke unit) and operational research into optimization of these transport models. It is hoped that the discussion can stimulate the readers to design a transport model to meet their local needs. Some of the papers in this special issue have source codes and data available for the adventurous readers to explore. Happy mapping and modeling.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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BRIEF RESEARCH REPORT
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The Large ARtery Intracranial Occlusion Stroke Scale: A New Tool With High Accuracy in Predicting Large Vessel Occlusion

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Objectives: The combination of systemic thrombolysis and mechanical thrombectomy is indicated in patients with ischemic stroke due to a large vessel occlusion (LVO) and these treatments are time-dependent. Rapid identification of patients with suspected LVO also in a prehospital setting could influence the choice of the destination hospital. Aim of this pilot study was to evaluate the predictive role of a new stroke scale for LVO, comparing it to other scores.

Patients and Methods: All consecutive patients admitted to our comprehensive stroke center with suspected ischemic stroke were studied with a CT angiography and 5 different stroke scales were applied. The Large ARtery Occlusion (LARIO) stroke scale consists of 5 items including the assessment of facial palsy, language alteration, grip and arm weakness, and the presence of neglect. A Receiving Operating Characteristic curve was evaluated for each stroke scale to explore the level of accuracy in LVO prediction.

Results: A total of 145 patients were included in the analysis. LVO was detected in 37.2% of patients. The Area Under Curve of the LARIO score was 0.951 (95%CI: 0.902–0.980), similar to NIHSS and higher than other scales. The cut-off score for best performance of the LARIO stroke scale was higher than 3 (positive predictive value: 77% and negative predictive value: 100%).

Conclusion: The LARIO stroke scale is a simple tool, showing high accuracy in detecting LVO, even if with some limitations due to some false positive cases. Its efficacy has to be confirmed in a pre-hospital setting and other centers.

Keywords: stroke, pre-hospital scale, large vessel occlusion, thrombolysis, mechanical thrombectomy

INTRODUCTION

The combination of systemic thrombolysis and mechanical thrombectomy is indicated in patients with ischemic stroke due to a large vessel occlusion (LVO), and this recommendation has been validated by previous randomized controlled trials (1–4). However, because stroke is a time-dependent disease, the benefit of these treatments is highly influenced by rapid identification of symptoms in the pre-hospital setting and concomitant fast transportation to comprehensive centers, which have limited beds and resources. For this reason, the concomitant time sensitivity for both treatments could influence the choice of the destination hospital. In recent years, several scales have also been applied to select patients with suspected stroke due to a large vessel occlusion in a pre-hospital setting. A recent meta-analysis of these studies showed a great heterogeneity of results with the best prediction observed for some scales (5), even if all presented a lower accuracy than the National Institute of Health Stroke scale (NIHSS) (6), and for this reason they presented several limitations in their application in a real-world setting. According to these evidences, the vessel images are mandatory to select patients for mechanical thrombectomy as they detect LVO with higher accuracy.

Aim of this pilot study was to improve the prediction of large vessel occlusion, assessing a new tool called Large ARterial Intracranial Occlusion (LARIO) Stroke Scale.

TABLE 1 | The LARIO Stroke Scale.

Item	Score
FACIAL PALSY	
Normal	0
Present	1
ARM WEAKNESS	
No drift	0
Drift or no effort against gravity or no movement	1
GRIP STRENGTH	
Normal	0
Reduced or absent	1
LANGUAGE	
Normal	0
Changes or global aphasia, or mute	1
NEGLECT	
Absent	0
Extinction to bilateral simultaneous stimulation in one or more sensory	1
Modality or an unrecognized own hand or orientation only to one side of the body	

LARIO, Large ARtery Intracranial Occlusion.

MATERIALS AND METHODS

Subjects

All patients admitted consecutively to our hospital between April and October 2017 with suspected ischemic stroke and with a brain CT scan excluding hemorrhage were also studied with a CT angiography of extra- intracranial arteries after a given written informed consent. At hospital arrival, different stroke scales have been administered to all patients by a single neurologist with a separate evaluation of a trained nurse using only the new tool. We excluded from this analysis patients with symptoms over 24 h or if the iodinated contrast agent administration was contraindicated (see flow-chart in **Supplemental Material**). The assessment order of stroke scales was: LARIO, Cincinnati Prehospital Stroke Severity Scale (CPSSS) (7), Los Angeles Motor Scale (LAMS) (8), Vision, Aphasia, Neglect assessment (VAN) scale (9), and NIHSS. For each patient, we registered also gender, age, stroke etiology, and the clinical syndrome, using TOAST and OCSP criteria.

Tool Assessment

The LARIO stroke scale was designed on the basis of the LAMS, adding "Neglect" as new item to this scale. LAMS was chosen because this tools showed high accuracy to detect LVO in previous studies and a concomitant simple assessment in a pre-hospital setting (5, 8). We added the evaluation of spatial cognition on the basis of our previous findings that showed a higher prediction of LVO using this variable than other items (5). In our scale we evaluated facial palsy, arm weakness, grip weakness, language alteration (aphasia or dysarthria), and finally presence of neglect (reported as an extinction to bilateral simultaneous stimulation in one or more sensory modality or an unrecognized own hand or orientation only to one side of the body). For each item we gave a score of 0 if absent and 1 if present (**Table 1**). We calculated the score with a possible range between 0 (normal) and 5 (maximum). The training for the nurse was planned using the online software for NIHSS certification with a particular attention to the evaluation of the neglect (www.nihss-neurosapienza.trainingcampus.net/) and it took about 1 week.

Image Protocol and Review

Two expert neurologists with certified vascular and radiological experience reviewed all images of brain CT and CT Angiography. They were blinded to patients' demographic and clinical data and they had not participated to the assessment of the scales. For each image, vessels were evaluated and graded for the presence or absence of a total occlusion and its site (intracranial internal carotid artery, the M1 and M2 tracts of the middle cerebral artery (MCA) and basilar artery).

Aim of the Study

The principal aim of this pilot study was the validation of a new screening tool detecting LVO in ischemic stroke patients, exploring also its level of accuracy compared with other scales. The secondary aim was to investigate the agreement level of the LARIO scores between the neurologist's and nurse's evaluations.

Sample Size Calculation

We estimated a sample size for adequate sensitivity and specificity, using the formula:

$$n = \frac{Z^2_{\frac{\alpha}{2}} \hat{P}(1 - \hat{P})}{d^2} \quad (1)$$

We postulated a sensitivity of about 0.80 and a specificity of 0.90 from previous study concerning the accuracy of LAMS score (5). At the same time, we assumed a marginal error of 0.10 and a prevalence of LVO in ischemic stroke patients of about 0.35–0.40.

By these parameters, we obtained the number of 141 as sample size calculation.

Statistical Analysis

Categorical variables were reported as proportions, while continuous variables were presented as median and interquartile ranges (IQR). We applied the chi-squared and *t*-test to compare categorical and continuous variables between groups. Receiver operating characteristic (ROC) curve analysis was applied to test the discrimination ability and the grade of accuracy of our scale applied by neurologist to predict a LVO, compared to the other tools. Sensitivity, specificity, positive, and negative predictive values were calculated for the new scale at different threshold. The Youden Index was used to calculate the optimal threshold of the LARIO stroke scale. Finally, we compared the sensitivity, specificity, and accuracy of the new scale at predefined score with other scales at prespecified published thresholds. The Cohen's k test was used to verify the degree of agreement between the scores of the LARIO stroke scale performed by the neurologist and nurse. We considered significant a p-value < 0.05. All statistical analysis were performed using SPSS software.

RESULTS

One hundred forty-five qualifying patients with ischemic stroke were selected. The median age was 77 years (IQR: 68–83) with prevalence of males equal to 60.7%. A LVO was detected in 54 patients (37.2%) with prevalence for the MCA of 43% (**Table S1**). The median score for the NIHSS was 7 (IQR: 4–17), while the LARIO stroke scale had a median score of 3 (1–4). The scores of the other applied scales are presented in **Supplementary Material**. While in the absence of LVO we observed low median scores of the different scales (from 0 of LAMS to 5 of NIHSS), in patients with LVO, the NIHSS, the LARIO stroke scale, the CPSSS, and the LAMS had, respectively, scores of 18, 4, 3, and 4. Considering the presence of LVO, we observed a significant difference in age (79 vs. 73; $p < 0.05$), but not for gender. Median onset-to-door time was 84 min (58–121) and time between assessment and CTA was 5 min (2–8).

The LARIO stroke scale showed a similar accuracy to the NIHSS in predicting LVO and a higher accuracy than the other scales. In particular, the area under curve (AUC) for our scale was 0.951 (95%CI: 0.902–0.980), while NIHSS showed an AUC of 0.915 (0.587–0.955). The ROC curve is represented in the **Figure 1**. The AUC of LARIO stroke scale was higher in the left hemispheric stroke than right cerebral ischemia (0.966 vs. 0.932), counting 36 patients with left stroke due to LVO (54 subjects had not a LVO) and 19 patients with right stroke and LVO (36 subjects had no LVO). However, the findings were significant in both sides. Pairwise comparisons of ROC curves confirmed the superiority of accuracy of NIHSS and LARIO on the other scales and a no-significant difference between the two tools (**Table S3**). According to the Youden Index, the best performance of the LARIO stroke scale was observed at the score superior to 3. At this criterion we calculated a sensitivity of 1 and a specificity of 0.82. The comparison of accuracy at this level of the LARIO stroke scale with other tools is showed in **Table S6**. While NIHSS administration was time consuming (mean time: 3.4 min; S.D.: 4.3 min), the administration of the LARIO stroke scale was faster (mean time: 1.2; S.D.: 3.2).

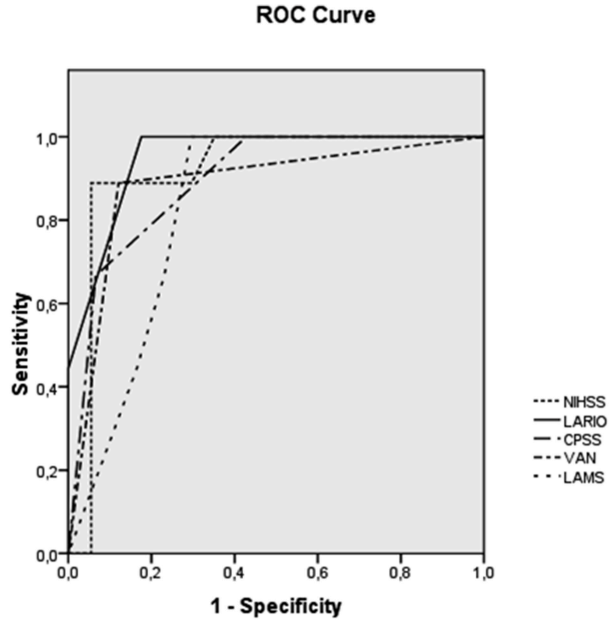
Finally, we observed a high agreement between the neurologist's and nurse's scores of the LARIO stroke scale (Cohen's k: 0.963; S.E.: 0.012; 95%CI: 0.940–0.986; $p < 0.001$).

DISCUSSION

In this pilot study, we observed that the LARIO Stroke scale at the best-calculated cut-off score has a high sensitivity and high specificity for the detection of LVO. In our trial, the rate of this condition was higher than in other studies, but it is in line with the prevalence of a very recent systematic review (10). However, our observation could also be due to a referral bias into the study. The Youden index showed the best prediction of LVO for a score of more than 3. At this cut-off score, the LARIO Stroke scale showed a significantly higher discrimination of patients with LVO when compared with the other scales, NIHSS excluded. A recent study showed a good identification of LVO patients using the CPSSS, with a ROC of 0.64. In the present study, the CPSSS had a higher value of ROC than the previous one, but lower than the new scale (11). In a previous review, we detected the best accuracy in detecting LVO for VAN, LAMS and NIHSS (5). However, in our sample we observed lower values for sensitivity and specificity for the VAN scale and a significant difference in the comparison of ROC curves, as well as for the LAMS scale. The remaining scale represented by the NIHSS showed similar results to the LARIO Stroke scale in detecting LVO. However, the NIHSS could be too complex for a pre-hospital setting in terms of time consumption and expertise of users. In light of these observations, our new scale appears simple to apply also for non-specialist professionals and with a limited time of application. Even though neglect is probably one of the most complex issues to assess, and one which carries a high chance of wrong interpretation by a non-neurologist, in our study we observed a significant agreement between neurologists' and nurses' evaluations of this condition. According to this observation, specific and effective training concerning the detection of this item could represent the crucial point for a correct assessment of the neglect.

Considering the different territories of LVO, in our pilot study the new scale also showed possible prediction for basilar occlusion because all six patients with this condition had a positive score on the LARIO Stroke scale. However, this observation needs to be confirmed with a greater sample. A limitation of the new tool could be an isolated or combined visual or cerebellar deficit, because these are not included in the assessment of the LARIO Stroke scale. However, basilar occlusion is unlike a condition of an isolated symptom; rather, several signs, and deficits are often reported (12, 13). At the same time, the presence of language and neglect assessments in the LARIO Stroke scale contributed to avoiding a failed detection of an MCA occlusion.

Recent European and American recommendations indicate that clinical screening tools may be introduced to facilitate the



SCALE	AUC	S.E.	95%CI	p
LARIO	0.951	0.013	0.902–0.980	reference
CPSSS	0.896	0.022	0.834–0.940	0.001
NIHSS	0.915	0.026	0.857–0.955	0.103
LAMS	0.832	0.033	0.760–0.888	< 0.001
VAN	0.884	0.028	0.820–0.931	0.004

FIGURE 1 | ROC curves comparing different stroke scales.

selection and triage of patients with suspected LVO who could be directly transferred to a comprehensive stroke center (14, 15). However, as vessel images detect LVO, they cannot be replaced by stroke scales in selecting patients for mechanical thrombectomy. Even if stroke scales showed high accuracy, they would have a significant false positive rate, as shown in the present pilot study (16, 17).

This could be one of the study limitations, but, even though we observed a false positive rate of 18%, no false negative cases were observed. A second limitation could be the setting in which it was applied (in-hospital and not extra-hospital) and the raters that applied the new scale. However, this is a pilot study and we observed a high accordance between scores obtained from neurologists' and nurses' evaluations after a brief training session that could be applied also for volunteers of the emergency medical services. Third, this scale is not able to differentiate ischemic from haemorrhagic strokes, but the direct transfer of severe patients with brain hemorrhage could benefit from a comprehensive stroke center with more facilities than a primary stroke center. Finally, we observed a 37.2% of LVO that indicates a prevalence rate higher than in population-based settings, and this result could be influenced by a referral bias, as previously mentioned.

There are some strengths for this new tool. First, it is quite simple and user-friendly after brief and effective training. Second, our pilot study to validate this scale was prospective with consecutively enrolled ischemic stroke patients. Third, all patients were studied with CT angiography with external validation of imaging.

CONCLUSION

Effective pre-hospital triage and organization for severe strokes have to reduce both the symptom onset-to-groin puncture time and hospital-to-hospital transfers. According to these aims, our scale could provide a significant response to the need for the use of an effective tool to optimize the triage of stroke patients suspected of LVO. These findings are preliminary to a new study assessing the feasibility of the LARIO Stroke Scale in a pre-hospital setting, including a larger sample of patients and the application by a wide variety of providers, also in other hospital centers.

ETHICS STATEMENT

The study was part of the routine clinical activity, adding the application of the new scale. Each patient signed a written consent for radiological examination and for anonymous general use of data concerning the hospitalization, according with local governmental acts.

AUTHOR CONTRIBUTIONS

SV and EA conceived and designed the study. SV and LF obtained the data for the work. ML analyzed the data. SV, ML, and EA interpreted the data for the work. SV drafted the work and ML and EA revised critically the paper for important intellectual content. All authors approved the final version of the paper to be published and agreed the accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00130/full#supplementary-material

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REVIEW
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Pre-hospital Assessment of Large Vessel Occlusion Strokes: Implications for Modeling and Planning Stroke Systems of Care

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The social and financial burden of stroke is remarkable. Stroke is a leading cause of death and long-term disability worldwide. For several years, intravenous recombinant tissue plasminogen activator (IV rt-PA) remained as the only proven therapy for acute ischemic stroke. However, its benefit is hampered by a narrow therapeutic window and limited efficacy for large vessel occlusion (LVO) strokes. Recent trials of endovascular therapy (EVT) for LVO strokes have demonstrated improved patient outcomes when compared to treatment with medical treatment alone (with or without IV rt-PA). Thus, EVT has become a critical component of stroke care. As in IV rt-PA, time to treatment is a crucial factor with high impact on outcomes. Unlike IV rt-PA, EVT is only available at a limited number of centers. Considering the time sensitive benefit of reperfusion therapies of acute ischemic stroke, costs and logistics associated, it is recommended that regional systems of acute stroke care should be developed. These should include rapid identification of suspected stroke, centers that provide initial emergency care, including administration of IV rt-PA, and centers capable of performing endovascular stroke treatment with comprehensive periprocedural care to which rapid transport can be arranged when appropriate. In the pre-hospital setting, the development of scales easier and quicker to perform than the NIHSS yet with a maintained accuracy for detecting LVO strokes is of paramount importance. Several scales have been developed. On the other hand, the decision whether to transport to a primary stroke center (PSC) or to a comprehensive stroke center (CSC) is complex and far beyond the simple diagnosis of a LVO. Ongoing studies will provide important answers to the best transfer strategy for acute stroke patients. At the same time, the development of new technologies to aid in real time the decision-making process will simplify the logistics of regional systems for acute stroke care and, likely improve patients' outcomes through tailored selection of the most appropriate recanalization strategy and destination center.

Keywords: stroke, large vessel occlusion, pre-hospital assessment, stroke triage, stroke systems of care

INTRODUCTION

The social and financial burden of stroke is remarkable. Stroke is the second leading cause of death and the first cause of long-term disability worldwide (1). Approximately 795,000 people experience a new or recurrent stroke in the United States each year and 40% are left with permanent disability (1, 2). Access to reperfusion therapies has changed the landscape of stroke care with dramatic improvements in functional outcomes as measured by the modified Rankin scale (mRS). However, the benefits of both intravenous recombinant type plasminogen activator (IV rt-PA) and endovascular therapy (EVT) are strongly time dependent.

At the pre-hospital setting, the primary goal for emergency medical services (EMS) is to ensure that stroke patients receive the fastest and most appropriate triage in order to optimize their chances of receiving reperfusion treatment. Nonetheless, EVT, a more effective treatment for large vessel occlusion (LVO) than IV rt-PA, is available only in a few centers. The contrasting efficacy for different types of ischemic strokes and the imbalance of the availability of treatments lead to a complex decision where time to treatment has to be weighed against effectiveness in any given clinical scenario.

In this article, we will discuss different aspects involved in the complex decision-making process for pre-hospital assessment and triage of stroke patients as well as current trends that will probably impact future directions in the field.

THE EVOLVING FIELD OF REPERFUSION THERAPIES IN ACUTE ISCHEMIC STROKE

For almost 20 years, IV rt-PA remained as the only proven therapy for acute ischemic stroke. In the NINDS rt-PA trial, the number needed to treat (NNT) for one additional 90-day excellent functional outcome (mRS ≤ 1) with IV rt-PA in the $\leq$ 3-h-window was 8.4 (3). In the ECASS-3 trial, the NNT with IV rt-PA in the 3–4.5-h-window for one additional 90-day excellent functional outcome was 20 (4). While IV rt-PA remains a level-IA treatment for acute ischemic stroke, it was early recognized its limited efficacy for LVO (5). In a recent published prospective study using CTA (median time of 132 min from the start of IV thrombolysis to reassessment), the frequency of recanalization of intracranial-ICA, proximal MCA-M1, distal MCA-M1, and MCA-M2 occlusions after IV t-PA was 18.1, 24.2, 17.9, and 32%, respectively (6).

Recent trials of EVT for LVO strokes have demonstrated improved patient outcomes when compared to medical therapy alone (with or without IV rt-PA). The development of endovascular approaches with stent-retrievers and/or thromboaspiration devices have made significant improvements in the treatment of LVO strokes with an average frequency of recanalization of 71% and major functional improvements including those patients with contra-indications for IV rt-PA (7, 8). The frequency of functional independence at 90 days (mRS ≤ 2) ranged from 32.6% up to 71% probably reflecting the type of imaging selection of patients and increased recanalization rates (9–13). As such, EVT has become an essential component of stroke care (5).

The progression of the penumbra to irreversible ischemia is not uniform across patients. Approximately 20–30% patients with LVO stroke fall within the spectrum of ultrafast progressors who may be at particular risk to develop accelerated ischemia with a malignant profile. However, a small proportion of patients ($\leq$30%) are "slow progressors" and can sustain adequate brain perfusion through an extended period allowing for reperfusion at later time windows with sustained benefits (14). A new milestone in the treatment of acute ischemic stroke was the extension of the therapeutic window for EVT up to 24 h in carefully selected patients who have LVO and salvageable brain, defined either by imaging mismatch (diffusion and/or perfusion techniques to evaluate ischemic core and penumbra on MR or CT) or by clinical-imaging mismatch with comparable treatment effects as earlier time windows. Even though patients were treated in an extended time window, the NNT for achieving functional independency at 90 days was 2.8 (absolute difference in the utility weighted mRS 2.1, 95% CI [1.2–3.1]) and 3.6 (OR 2.77; 95% CI [1.63–4.70]) in the DAWN and DEFUSE-III trials, respectively (15, 16).

After several failed attempts, intravenous thrombolysis has also recently experienced a stretch in its therapeutic time window. Based on FLAIR-DWI mismatch the MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset (WAKE-UP) trial showed benefit (mRS ≤ 1 at 90 days) of IV rt-PA for patients with more than 4.5 h from last seen well (OR 1.6, 95% CI [1.1–2.4]; $p = 0.02$) with an acceptable safety profile (17). The EXTEND trial used perfusion imaging to select patients for IV thrombolysis up to 9 h from stroke onset. Patients assigned to treatment were more likely to achieve excellent functional outcome at 3 months (adjusted risk ratio, 1.44; 95% CI [1.01–2.06]; $P = 0.04$) with a rate of symptomatic ICH similar to trials of earlier time windows (adjusted RR, 7.22; 95% CI [0.97–53.54]; $P = 0.05$) (18).

The development of new thrombolytic agents has also contributed to lighten the path of reperfusion therapy in acute ischemic stroke. Tenecteplase (TNK), a modified plasminogen activator with higher fibrin specificity with superior pharmacodynamic and pharmacokinetic properties, was recently compared with alteplase showing improved functional outcomes and higher recanalization rates when compared to IV rt-PA prior to EVT (19). Its efficacy, lower cost, and the simplified logistics associated with a single bolus dose of TNK will likely play an important role in the acute stroke treatment. These advantages make TNK an interesting candidate for use in mobile stroke units which have consistently shown to reduce delays in treatment (20–22).

The recent advances in reperfusion therapy have allowed for an expansion of its benefit to a larger population of patients. However, time to treatment remains a crucial factor with high impact on outcomes in both treatment modalities. The frequency of good outcome after IV rt-PA treatment decreases rapidly with time. The NNT to achieve excellent functional outcome (mRS 0–1) at 90 days rises from 4.5 to 9 and 14.1 for those patients treated within 90, 91–180, and 181–270 min, respectively (23). The same reasoning can be applied to EVT in broadly selected patients with frequencies of good functional outcome (mRS 0–2) ranging from 64.1% for those reperfused within 180 min to 46.1% for those reperfused within 480 min (24).

Some patients may still have mismatch between the amount of critically hypoperfused and infarcted brain at the extended window and may therefore benefit from reperfusion at later times (as shown in DAWN and DEFUSE 3 trials). However, the chances of having a significant mismatch decay over time. As such, the importance of time remains as one of the pillars of stroke emergency care together with effective reperfusion.

TRIAGE OF STROKE PATIENTS IN THE PRE-HOSPITAL SETTING

Considering the time sensitive benefit of reperfusion therapies of acute ischemic stroke as well as the costs and complex logistics associated, it is highly recommended that regional systems of acute stroke care should be developed. These should include centers that provide initial emergency care, including administration of IV rt-PA, and centers capable of performing EVT with comprehensive periprocedural care to which rapid transport can be arranged as appropriate (5).

For pre-hospital patients with suspected LVO by a stroke severity scale, the decision whether to transport first to a primary stroke center (PSC) and then to a comprehensive stroke center (CSC)—drip-and-ship model (DS)—or directly to a CSC—mothership model (MS)—is multifactorial. A critical factor is to define whether, by the time the patient gets to the closest PSC vs. CSC, he/she will be a candidate to IV rt-PA only, EVT only, both, or neither one. It thus becomes essential to understand the untoward consequences of suboptimal triage as (1) bypassing the closest PSC to a CSC may (a) decrease the chances of the patient receiving IV rt-PA, (b) prolong the time to IV rt-PA treatment, and (c) unnecessarily saturate the CSC bed capacity with patients that could be well-cared for at a closer PSC, and (2) going to the closest PSC may prolong the time to EVT or even completely preclude its performance.

One variable to be considered is time from stroke onset (or time last seen well if the ictus was unwitnessed or upon awakening). As previously mentioned, time is a strong determinant for the IV rt-PA therapeutic response in stroke. Indeed, the first hour after stroke onset, as in trauma care, has been coined as the "golden hour" for reperfusion therapies and is associated with a higher proportion of patients with favorable and excellent outcome in all age groups (8, 25). As a consequence, if a patient has the possibility to be treated within 1 h of onset, this is a variable that should be taken into account and the patient should be transported to the nearest rt-PA-capable hospital. Having said that, one must also consider any potential rt-PA exclusion criteria in the decision algorithm for the best primary destination stroke center. Moreover, no specific data is available regarding the effect of IV rt-PA during the golden hour in LVO patients, so its impact on the line of care is yet to be established.

Mixed results have been reported in the literature. Some studies have shown added benefit of early IV thrombolysis before thrombectomy in LVO stroke patients in terms of recanalization and functional outcomes (19, 26). Nevertheless, a recent systematic review favors the MS model over the DS for patients with suspected LVO. Those patients that were primarily direct to a CSC (MS model) had significantly better outcomes than patients that were first directed to a PSC and then transferred to a CSC (DS model) (90-day mRS 0–2: 60.0% vs. 52.2%; OR, 1.38; 95% CI [1.06–1.79]; $p = 0.02$). Even though, no difference was found between the treatment pathways in successful reperfusion, patients undergoing MS had better functional outcome than those undergoing DS, probably as a consequence of quicker transfer times (that could go up to 100 min in the DS model) and shorter time-to-reperfusion, known to be a powerful predictor of good outcome (27). However, these are retrospective studies and the results must be interpreted with caution.

Likewise, during inter-hospital transfer, one out of three patients with stroke from anterior circulation LVO becomes ineligible for mechanical thrombectomy (MT) due to progression of ischemic core based on CT ASPECTS imaging criteria (28). This highlights the critical importance of better field triage and rapid transfer for patients with LVO profile to hospitals capable of carrying out MT. Therefore, it is of paramount importance the expeditious transfer process for patients with LVO, which are primarily admitted to a PSC.

The time from PSC arrival to PSC departure (e.g., door in door out; DIDO) has become just as critical of a metric as the door-to-needle (DTN) time. Implementation of organized protocol for interhospital transfer of patients should be established and approved in PSCs, since it is associated with a reduction of PSC DIDO times arrival to the CSC and probably faster reperfusion. One example of such a protocol led to shorter DIDO time (64 vs. 104 min) which explained much of the reperfusion time (132 vs. 179 min). As consequence, patients were twice as likely to have a favorable outcome (OR 2.99 [95% CI, 1.0–8.7]; $p = 0.04$) (29).

Another point to be considered, is the transport times to a PSC or to a CSC as well from the PSC to the CSC. The decision about the most suitable type of transportation (ground, air, or even water transport) depends not only on the distance but also traffic conditions (which varies according the time of the day), climatic (e.g., rain, snow, storms), and geographic barriers (e.g., mountain, rivers, sea) as well as the need for critical care support during transport and the cost-benefit of the different options.

In the same direction, it has also become critical to consider the degree of efficiency across the different PSCs and CSCs by carefully tracking key workflow and performance metrics including (but not limited to) their DTN and door-to-reperfusion times. For instance, in the regional scenario where a highly efficient CSC has DTN times 20 min shorter than the closest PSC, a direct transfer to the CSC might be the preferable approach even if that means that bypassing the PSC would result in a transportation time that is 15 min longer. In cases of high probability of LVO, even longer transportation delays could be justifiable. In contrast, if a PSC has short DTN time and CSC has long DTN and door-to-reperfusion times, the DS model may be favored.

Notably, there are five ongoing randomized trials comparing primary EVT vs. bridging therapy for patients directly presenting to thrombectomy capable centers. These include the SWIFT-DIRECT trial in Europe and Canada, the DIRECTSAFE trial in Australia, the SKIP in Japan, the DIRECT-MT trial in China, and the MRCLEAN No-IV trial in the Netherlands. These trials will provide critical insights about the differences in safety, efficacy, and cost-effectiveness across these two approaches and their results may lead to significant changes in the current field triage algorithms.

At the moment, there is no evidence to address the question of which patient transfer option is ideal e.g., MS or DS. The RACECAT trial is a prospective, multicenter, cluster randomized study in Catalonia territory that aims to evaluate whether a pre-hospital triage system to determine either a nearest rt-PA-capable hospital or bypass the closest facility to bring the patient to one that offers EVT (DS vs. MS), increases the efficiency of reperfusion treatments and leads to better long-term functional outcomes. Results of RACECAT will provide important answers to many of our current dilemmas (30). In addition, PRESTO (Pre-hospital Routage of acute Stroke Patients with Suspected Large Vessel Occlusion), is a French phase III randomized trial that will compare mother-ship vs. drip-and-ship strategies in terms of QUALYs (31). The results of these trials will provide important answers to many of our current dilemmas. While, stroke networks share similar issues, the results will have to be thoughtfully studied, compared, and adapted before full implementation in other stroke networks as many do not share the same organization, financial, and geographical conditions.

In each regional network, we can identify variables that favors MS or DS transfer models, so customization of the guideline to optimize patient selection for MS or DS will be needed and must take into account many local and regional factors, including: (1) time from stroke onset (or TLSW), (2) potential contraindications for IV rt-PA, (3) likelihood of LVO; (4) availability of PSC and CSC, (5) transport times to PSC or to CSC, (6) door in–door out times for PSC, (7) transfer time from PSC to CSC, (8) DTN (PSC and CSC) and door-to-reperfusion (CSC) times, and (9) EVT performance metrics (rates of reperfusion, favorable outcomes, symptomatic intracranial hemorrhage and other periprocedural complications, and mortality). Collaborative quality review processes involving regional EMS agencies and hospitals is therefore highly recommended for the development of operationalized bypass algorithms based on maps that consider all the aforementioned variables, according to each regional reality (32).

Applying different transportation paradigms to interventional stroke management are also possible. Other time sensitive procedures such as organ harvest have transported physicians to the patient site to improve time to procedure. Applying this same principle to interventional stroke management, lead to important time delay reductions in a proof of concept study (33).

Currently, a major challenge for pre-hospital care is the development of triage protocols to ensure that patients with a suspected stroke are rapidly identified and those with LVO profile are promptly recognized through the use of validated and standardized pre-hospital scales for stroke screening.

PRE-HOSPITAL SCALES TO DETECT LARGE VESSEL OCCLUSION ISCHEMIC STROKE

The public health impact of thrombectomy is highly dependent on rapid identification of severe stroke symptoms by EMS personnel and transport to a CSC with experience in providing fast, effective, and safe interventions. Despite the major therapeutic improvement, only a limited number of hospitals are EVT capable.

If a prediction instrument could reliably identify LVO in the field, those patients could be transported directly to EVT-capable hospitals, bypassing PSC and avoiding unnecessary delays. Another possibility would be that for patients with high suspicion of LVO, the same EMS team that brought the patient to the PSC could wait on site for a rapid assessment and treatment including IV rt-PA if eligible and then more promptly transfer the patient to a CSC as this would obviate the need to wait for new transportation team.

The NIHSS was found to be predictive of anterior circulation LVO strokes. For patients with <3 h from symptom onset, NIHSS scores ≥ 9 had positive predictive value of 86.4% and for patients between 3 and 6 h NIHSS scores ≥ 7 had a positive predictive value of 84.4% for LVO (34). In a recent study, of the 97 patients with suspected acute stroke (RACE score performed by EMS personnel ≥ 4) presenting to a CSC within the first 6 h from onset with NIHSS score > 10 on arrival, 11 (11.6%) had intracerebral hemorrhage and seven (7.2%) had no LVO after angiographic evaluation resulting a rate of LVO detection of 76.3% (35). Nonetheless, the NIHSS requires a greater degree of training, is too time-consuming to be performed in the pre-hospital setting and has only been validated for stroke severity assessment in the hospital environment.

As a result, it has become critical to develop objective pre-hospital triage criteria that appropriately identify patients who are most likely to benefit from services only available at CSC and therefore should be considered for direct transportation, while also facilitating the proper triage of less complex or lower acuity patients to the nearest stroke center (5, 36).

Several stroke severity scales aimed at recognition of LVO strokes in the pre-hospital setting have been published (**Table 1**) (37–43). They were initially derived from data sets of confirmed stroke cases or selected pre-hospital cases, and there has been only a limited number of prospective studies for their validation.

The performance of most available scales based on published literature was recently compared. However, at this time, there is insufficient evidence to recommend one scale over the other or a specific threshold of additional travel time for which bypassing a PSC or acute stroke-ready hospital is justifiable. The utilization of EMS stroke scales to predict LVO lack both high sensitivity and specificity, resulting on overtriage or missed cases. Moreover, it is unlikely that clinical assessment alone will have the required

TABLE 1 | Pre-hospital stroke scales and parameters assessed.

Clinical prediction tool	Parameters assessed
National Institutes of Health Stroke Scale (NIHSS)	
Cincinnati Pre-hospital Stroke Severity Scale (CPSSS) (37)	• Conjugate gaze deviation • Questions and commands • Arm weakness
Los Angeles Motor Scale (LAMS) (38)	• Facial droop • Arm drift • Grip strength
Rapid Arterial Occlusion Evaluation (RACE) (39)	• Facial palsy • Arm motor function • Leg motor function • Head and gaze deviation • Aphasia • Agnosia
3-item Stroke Scale (3-item SS) (40)	• Consciousness • Gaze and head deviation • Hemiparesis
Field Assessment Stroke Triage for Emergency Destination (FAST-ED) (41)	• Facial palsy • Arm weakness • Speech changes • Eye deviation • Extinction/neglect
Stroke Vision, Aphasia, Neglect (VAN) (42)	• Arm weakness • Visual disturbance • Aphasia • Neglect
Conveniently-Grasped Field Assessment Stroke Triage (CG-FAST) (43)	• LOC questions • Gaze • Facial palsy • Arm weakness • Speech problems

accuracy to diagnose LVO given the wide spectrum of symptom severity presented. Given the known impact of delays to both IV rt-PA and MT on outcome and the anticipated delays in transport for MT in eligible patients originally triaged to a PSC, the Lifeline Severity-Based Stroke Triage Algorithm was developed as an evidenced-based best-practice multi-specialty review of currently available data for EMS Stroke Triage and should be seen as broad guideline to more specific regional protocols (**Figure 1**) (44).

In the absence of new evidence, the Severity-Based Stroke Triage Algorithm for EMS endorses routing patients directly to CSC for clinical and transport scenarios fulfilling certain criteria. For those patients within 6 h of the time since last-known well, the algorithm favors direct transport to the nearest CSC if transport adds ≤15 min to transport compared with time to the nearest facility and this bypass does not preclude the use of IV rt-PA. The impact of the new trials of rt-PA beyond 4.5 h and those that address the benefit of use rt-PA or TNK prior to EVT will certainly affect the decision-making process of stroke triage. Customization of the guideline to optimize patient outcomes will be needed to account for local and regional factors, including the availability of endovascular centers, DIDO times for non-endovascular stroke centers, inter-hospital transport times, and DTN and door-to-puncture times.

NEW TECHNOLOGIES TO AID THE PRE-HOSPITAL ASSESSMENT AND DECISION MAKING

Considering the above-mentioned reasons, EMS field triage to stroke centers has gained considerable complexity. Simultaneously, system-wide implementation of transport algorithms in a stroke network is challenging. Proper selection of a destination stroke center will enhance appropriate resource utilization to meet the needs of individual patients to optimize time to reperfusion and the broader community by minimizing the time of ambulance use and distributing stroke patients more homogeneously to minimize the effects of crowding on a single healthcare system.

Although, field identification of potential candidates for MT is possible using stroke scales designed to recognize LVOS, the decision tree is substantially more complex because many of these patients are also candidates for IV rt-PA, which could often be more promptly provided at a closer location. Therefore, an optimal destination triage algorithm should not only include the probability of LVOS but also include information about the eligibility for IV rt-PA, real-time transportation time differences between CSC and PSC and the availability of human and material resources.

An ideal platform should permit customization for the needs a particular region, be cost free to the end user, and be broadly and easily available with great portability while offering a user-friendly interface and decision algorithm that decreases cognitive load. Applications designed for smartphones fulfill most of those characteristics. In fact, the use of smartphones has grown substantially among healthcare professionals and already has many different purposes in the area of stroke.

The FAST-ED (Field Assessment Stroke Triage for Emergency Destination) application is based on a built-in automated decision-making algorithm to assist EMS professionals with the decision about the most suitable destination for any given patient with acute ischemic stroke. It relies on (1) a brief series of questions assessing patient's age, anticoagulant usage, time last seen well, motor weakness, gaze deviation, aphasia, and hemineglect; (2) a database of all regional stroke centers according to their capability to provide endovascular treatment; and (3) Global Positioning System technology with real-time traffic information to compute the patient's eligibility for rt-PA or EVT as well as the distances/transportation times to the different neighboring stroke centers (45).

Effective communication is a highly valued attribute in a stroke network. Join (Allm Inc., Japan) is an application designed to simplify sharing of clinical and radiological medical information as well as to provide a platform for active communication. It offers a wide range of usages including: messaging, group chatting, integration with PACS system, streaming of live feed videos, and time tracking. It is also possible to provide integration with other applications such as the FAST-ED app thus providing support not only to effective communication but also to shared decision in complex situations.

Considering the limitations of pre-hospital scales for diagnosing LVO strokes given the wide spectrum of symptom

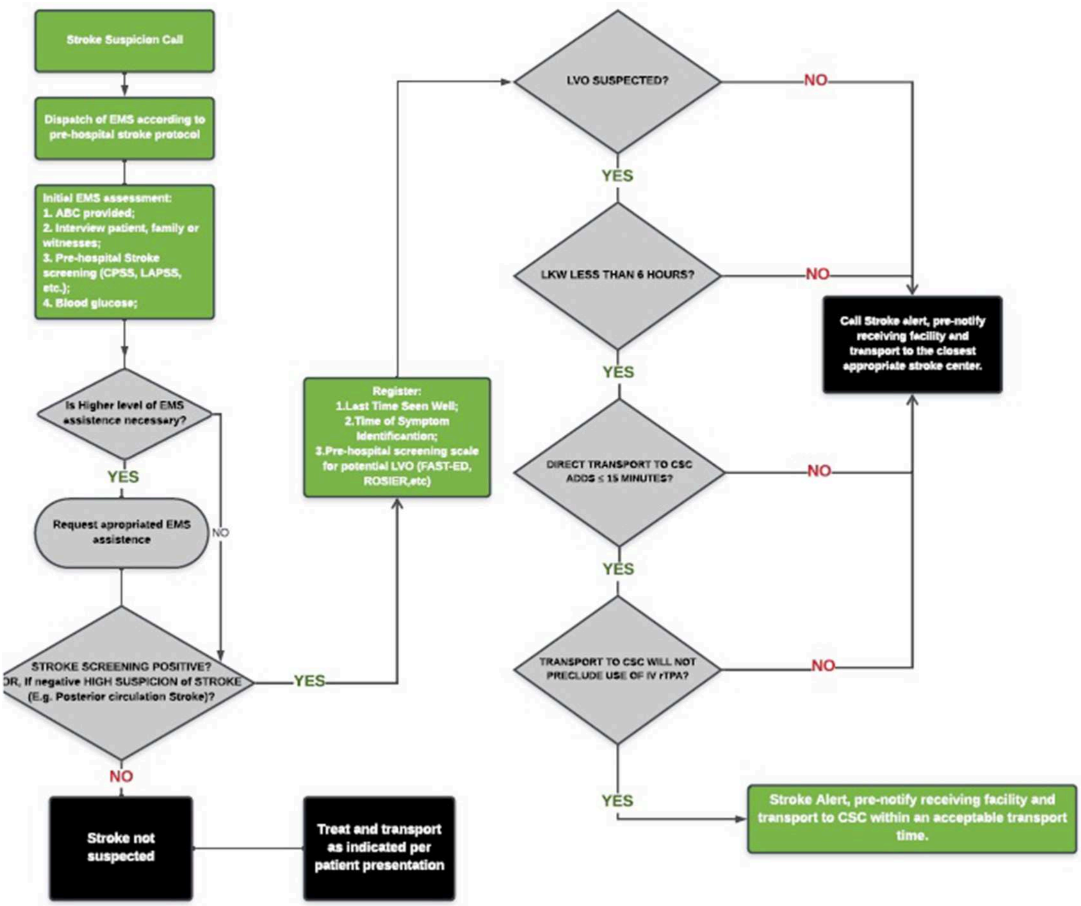

FIGURE 1 | Lifeline severity-based stroke triage algorithm for emergency medical services. *Adapted from Severity-Based Stroke Triage Algorithm for EMS (44).

severity, new technologies have been proposed and developed to increase triage accuracy. Transcranial Doppler (TCD) is a strong candidate for triage evaluation of LVO since is portable, non-invasive, has low cost and have been validated. However, it needs proper training and specialized personnel for reliably results. The Lucid Robotic System (Lucid M1 Transcranial Doppler Ultrasound System, Neural Analytics Inc., USA) is a robotically assisted ultrasound system for brain health assessment. It relies on evaluating the cerebral blood flow velocity (CBFV) morphology to compute a quantitative diagnostic metric called the Velocity curvature index (VCI). VCI has shown similar accuracy to the others specific TCD findings with LVO, and a recent study showed superiority of VCI over a standard Velocity Asymmetry Index (VAI) with accuracy of 88% and 79% to detect LVO, respectively. The SONAS (BURL Concepts Inc., USA) is a portable battery-powered TCD that utilizes ultrasound microbubbles as acoustic traces to detect LVO by an algorithm that evaluates brain perfusion semi-quantitatively, but it results have not been published yet.

An attractive strategy to expedite treatment and improve outcomes is the concept of "bringing the hospital to the patients." This strategy is based on the use of ambulances (mobile stroke units) equipped with imaging system (including CTA and CTP as new development), point-of-care laboratory, telemedicine connection, and appropriate medication. Studies of pre-hospital stroke treatment have consistently shown a reduction in delays before thrombolysis and in to the triage to the appropriate target hospital (e.g., primary vs. CSC) (3, 11, 22)

The volumetric impedance phase shift spectroscopy (VIPS) is a non-invasive device (Cerebrotech Medical Systems, Pleasanton, California, USA) that aims to detect hemispheric bioimpedance asymmetry. The fluid and electrolyte changes caused by brain ischemia produces alterations on electrical properties that modifies the cerebral bioimpedance signature on the affected hemisphere allowing the detection of severe strokes, including LVO, with a sensitivity of 93% and specificity of 92% although it does not separate out ischemic from hemorrhagic strokes.

New technologies for pre-hospital assessment including identification and proper triage of LVO is a fast-evolving field, that will definitively influence decision-making process and organization of stroke networks. Nonetheless, their usefulness is yet to be tested in RCT and real-life scenarios.

As new data comes into play, the pre-hospital assessment and management of acute stroke will continue to evolve, changing the way decisions are made nowadays. New technologies will have increasing influence either in improving diagnostic accuracy in the prediction of LVO strokes, in improving communication across stroke networks as well as aiding health care professionals in the multi-factorial decision-making process.

AUTHOR CONTRIBUTIONS

FL and RN conceived and wrote the manuscript. FM and DB made critical reviews of the manuscript.

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Application of Strategic Transport Model and Google Maps to Develop Better Clot Retrieval Stroke Service

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Background and purpose: Two hubs are designated to provide endovascular clot retrieval (ECR) for the State of Victoria, Australia. In an earlier study, Google Maps application programming interface (API) was used to perform modeling on the combination of hospitals optimizing for catchment in terms of current traveling time and road conditions. It is not known if these findings would remain the same if the modeling was performed with a large-scale transport demand model such as Victorian Integrated Transport Model (VITM). This model is developed by the Victorian State Government Transport has the capability to forecast travel demand into the future including future road conditions which is not possible with a Google Maps based applications. The aim of this study is to compare the travel time to potential ECR hubs using both VITM and the Google Maps API and model stability in the next 5 and 10 years.

Methods: The VITM was used to generate travel time from randomly generated addresses to four existing ECR capable hubs in Melbourne city, Australia (i.e., Royal Melbourne Hospital/RMH, Monash Medical Center/MMC, Alfred Hospital/ALF, and Austin Hospital/AUS) and the optimal service boundaries given a delivering time threshold are then determined.

Results: The strategic transport model and Google map methods were similar with the R^2 of 0.86 (peak and off peak) and the Nash-Sutcliffe model of efficiency being 0.83 (peak) and 0.76 (off-peak travel). Futures modeling using VITM found that this proportion decreases to 82% after 5 years and 80% after 10 years. The combination of RMH and ALF provides coverage for 74% of cases, 68% by 5 years, and 66% by 10 years. The combination of RMH and AUS provides coverage for 70% of cases in the base case, 65% at 5 years, and 63% by 10 years.

Discussion: The results from strategic transport model are similar to those from Google Maps. In this paper we illustrate how this method can be applied in designing and forecast stroke service model in different cities in Australia and around the world.

Keywords: stroke, transport, optimization, Google Maps, endovascular clot retrieval

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INTRODUCTION

The successes of endovascular clot retrieval (ECR) trials in 2015 (1–6) have generated optimism in the treatment of stroke and also debate on translating of these trials into clinical practice for both rural and metropolitan patients (7). These issues include whether patients should be transported to transfer directly to "mothership" or treat at the local hospital first, so called "drip and ship" (8, 9). Initial management at the local hospital has been associated with delayed onset to revascularization (10) and poorer outcome (11). Such idea on treatment exist previously in the development of primary stroke center (PSC) and comprehensive stroke center (CSC) (12, 13). Hospitals certified as CSC have faster time to reperfusion than PSC (14); these ideas now have taken center stage given the better outcome for ECR in centers with high volume output of cases. However, transfer of all cases or screened positive LVO cases can impact on capacity of the receiving hospital. The capacity of the "mothership" hospital to handle the diversion of patients has not been evaluated. In 2017, it has been estimated that 10–16% of patients would be eligible for ECR. This number will change with the publications of two ECR trials which extend the time window to 16–24 h (15, 16).

The State of Victoria had deemed in 2016 that two ECR hubs would be required for this purpose and performed a rigorous process to select the ECR hubs (17). This idea is similar to the concept of CSC but with a difference that the CSC provide care for the catchment and also outlying rural areas (12). Royal Melbourne Hospital (RMH) was selected as the first site with Monash Medical Center (MMC) added in the year 2018. An initial study showed that the combination of RMH and MMC would be optimal in terms of the ability of patients to travel to these hospitals within the idealized time of 30 min (18). This study was performed using an interface to the Google Maps API to query traveling time at different times of the day. A potential drawback of that study is that it cannot assess stability of the transport model in the future given population growth, increasing number of cars on the road and building of new road links and public transport routes. In this study, a trip-based travel demand model developed for the whole state of Victoria was used to obtain the travel time from a random generated address to each of the nominated ECR-capable hospitals in Melbourne. This method of analysis is standard within the transport industry but is not so well known in the medical literature, Historically, models of these systems have been developed to model the movement patterns of passengers and vehicles in cities. These models are used by transport planners and decision makers to understand the travel behavior of travelers over time (19). The aim of this study is to employ a strategic transport model to evaluate the findings from the Google Maps API and assess if the catchment for the two hospitals remain stable into the future. Consistent with the idea developed in the call for paper in this special issue of Frontiers in Neurology, we will spend the next section discussing how investigators can apply similar methods at their local sites.

METHODOLOGY

Setting

Melbourne is the second largest city in Australia and is the capital city of the state of Victoria in Australia with a population of approximately 4 million. The addresses were generated from the postcodes for metropolitan Melbourne are in the range 3,000–3,207. This aspect had been described in our earlier paper in 2017 (18).

ECR Capable Hospitals

There are 4 ECR capable hospitals in Victoria: Royal Melbourne Hospital (RMH), Monash Medical Center (MMC), Austin Hospital (AUS) and Alfred Hospital (ALF). At the time of the writing of the Statewide Protocol for ECR in 2017, it was planned to operate with 2 ECR hubs (17). RMH is located near to the center of Melbourne, MMC to the South-East, AUS to the North and ALF is located between RMH and MMC.

Transport Modeling

In this paper, an idealized time of 30 min is used based on the modeling in the redesign of stroke service in London (20). In this section, we explain the VITM model as a transport demand model as well as its functionality to generate the service boundaries of nominated ECR-hub in different combinations based on travel time. The Victorian Integrated Transport Model (VITM) is a large-scale trip-based model known as "four-step" process which has been used by the Victorian Department of Transport (DoT) and VicRoads to evaluate the impacts of alternative transportation and land use investments as well as presenting any changes in travel demand in response to different input assumptions (21). This process has four basic phases as its name implies: trip generation, trip distribution, mode choice and, trip assignment (22). This study consists of two main stages. The first stage is to validate the VITM model by comparing the VITM base case 2016 results with travel time data produced by the Google Maps API from the previous study. To this end, different statistical tests such as R^2, RMSE, and NSE will be applied. Once the validity of the VITM model is confirmed, VITM will then be utilized to predict travel time in projection years of 2021 and 2026.

VITM MODEL

Trip generation predicts the number of trips produced in a certain area of the network by trip purpose and destined for a particular traffic analysis zone. Trip distribution connects trip production and attraction. Mode choice defines if trip is done with personal vehicle or public transport while trip assignment estimates the specific route for each trip. The original VITM was developed based on the travel data collected during 1990 but recalibrated using the Victorian Integrated Survey of Travel and Activity (VISTA) data (23). VISTA is a household survey diary data of randomly selected households (23). In this data, all information about how individuals travel including a simple walk with their dog to the way they travel between states are gathered. The main goal of this survey is to understand the complex travel behavior of individuals. The model then incorporates the complex interactions within the transport system (e.g., car driving, public transport or other mobility modes) and that with economics, demographic and future land use change. The VISTA data was used in recalibration process to update trip generation, distribution and mode choice modules.

The state-wide version of VITM covers the entire state of Victoria. This model is based on a zone structure which collectively represent the geography of the modeled area. This model consists of 6,973 transport zones (12). The standard outputs from VITM are available at 5-yearly intervals from the latest VISTA data of 2016 year to a 30-year horizon (2046). This model provides travel demand estimates based on trip origin to destination, selected mode of car or public transport for all travel purposes. The car "skim" matrices produced by VITM represent travel time in minutes by time of day period as well as travel distance in form of kilometer by time of day.

Comparison of Different Models

Traffic zones containing the random addresses used in our previous study were identified, and travel time between each traffic zone and each hospital calculated using the VITM model. The catchment area for each hospital was determined by assigning each traffic zone to the closest hospital according to travel time. To estimate the catchment area of each hospital in 2-hub combinations, the number of zones which have travel time to that hospital less than the paired one were collected. The traveling time to 2-ECR combinations extracted from VITM in comparison to the Google Maps API data as well as the proportion of patients arriving to nominated hospital in each model during period are illustrated in **Table 1**. **Figures 1–3** show the catchment area of RMH as reference hospital in different combination with other hospitals.

The findings from Google Map were compared to that by VITM model using the R^2, and Nash–Sutcliffe model efficiency coefficient. The base case refers to the travel times extracted using Google APIs for Wednesday, 8th of June 2016 (24). The R-squared (R^2), and Nash-Sutcliffe model efficiency (NSE) are normally employed in model evaluation studies. R^2 values are within the range of 0 and 1 where values close to 0 show a poor fit and values close to 1 represent a perfect fit. The Nash-Sutcliffe model efficiency coefficient ranges from $-\infty$ to 1. An efficiency of 1 ($NSE = 1$) corresponds to a perfect match of the model (13, 14).

TABLE 1 | Proportion of patients arriving within 30 min in 2-hub models over base and future years.

Year \ Model	Model 1-a (RMH-MMC) (%)	Model 1-b (RMH-ALF) (%)	Model 1-c (RMH-AUS) (%)	
2016	82	65	63	Peak
2021	79	61	60	
2026	77	59	59	
Year \ Model	**Model 1-a**	**Model 1-b**	**Model 1-c**	
2016	86	74	70	Off peak
2021	82	68	65	
2026	80	66	63	

Stability of the Model in Future Year 2021 and 2026

Input variables to VITM for future years (2021 and 2016) consist of changes in land use data and generalized highway cost calculation including demographic, income growth, vehicle operating cost, parking cost, and parking boundaries. Following we will present results for the permutation of 2-hub in future years. Average time to each hospital in each combination as well as changes in proportion of patients arriving the hubs in critical 30 min during 10 years from 2016 to 2026 are presented inrea (**Table 1**).

RESULTS

For travel time forecasts, the strategic transport model and Google map methods had similar outputs with an R^2 of 0.86 (peak and off peak) and the Nash-Sutcliffe model of efficiency being 0.83 (peak) and 0.76 (off-peak travel).

Model 1-a (RMH, MMC) had a greater proportion of cases arriving to hospital within 30 min in all 3 years compared with model 1-b (RMH, ALF) and 1-c (RMH, AUS) (**Supplementary Table 1**). In model 1-a, the median traveling time to RMH is 15 min (IQR 17.75–23.08 min), 80% of cases within idealized travel time (TT) of 30 min during inter-peak in 2016 which decline to median travel time of 20.5 min (IQR 13.8–27.3) with 72% cases within TT. The same trend can be seen in MMC from 2016 to 2026 with increase in travel time from 15 (IQR 13.3–18.13) to 18.8 (IQR 14.3–23.35) and a decrease in percentage of cases arriving under 30 min from 90 to 85%. In other 2-hub models, the general decreasing trends in coverage of nominated hospital within 30 min are observable (**Supplementary Table 2**). In model 1-b, the median time to RMH was 21 min (IQR 17.75–23.08) in the year 2016, 25.84 min (IQR 19.16–32.53) in the year 2021 and 26.18 min (IQR 19.43–32.92) in the year 2026; the median time to ALF was 20 min (IQR 16.54–23.15) in the year 2016, 23.98 min (IQR 16.59–31.38) in the year 2021 and 24.09 (IQR 16.65–31.53) in the year 2026. In model 1-c, the median time to RMH was 15 min (IQR13.1–18.6) in the year 2011, 19.9 min (IQR13.28–26.65) in the year 2021 and 20.5 min (IQR 13.8–27.3) in the year 2026; the median time to AUS was 15 min (IQR 13.3–18.13), 16.13 min (IQR 13.93–18.33) in the year 2021 and 18.8 min (IQR 14.3–23.35) in the year 2026.

The combination of RMH and MMC has the greatest proportion of simulated cases arriving within ideal time of 30 min, 86% (off-peak) and 82% (peak). This proportion decreases to 82% (off-peak) and 79% (peak) after 5 years and 80% (off-peak) and 77% (peak) after 10 years. The combination of RMH and ALF provides coverage for 74% of cases, 68%

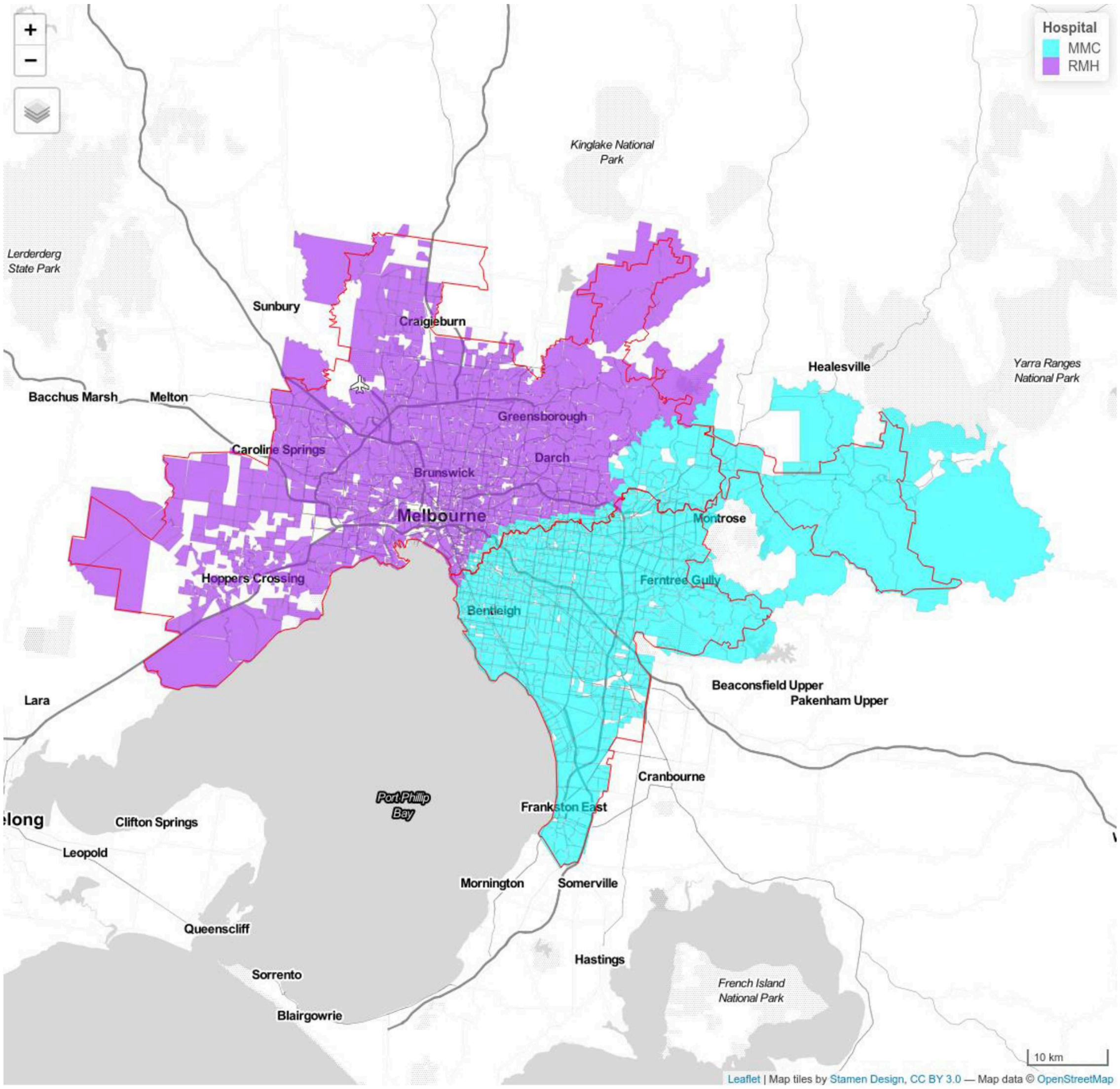

FIGURE 1 | Model 1a Royal Melbourne Hospital (RMH) and Monash Medical Center (MMC). Royal Melbourne Hospital's catchment has purple color and Monash Medical Centre's catchment is displayed with blue color. Red line shows the boundary determined using Google APIs.

by 5 years and 66% by 10 year. The combination of RMH and AUS provides coverage for 70% (off-peak) and 65% (peak) of cases in the base case, 65% (off-peak) and 61% (peak) at 5 year, and 63% (off-peak) and 59% (peak) by 10 year (**Table 1**).

Off peak, the VITM model yields a total of 4,338 patients within MMC catchment and 5,434 patients in RMH catchment. The Google Map model yields a total of 3,854 patients within MMC and 5,958 patients. If 10% of the patients with stroke in this catchment are eligible for ECR then it is estimated from VITM model that the number of cases in the MMC and RMH catchments are 434 and 543 patients, respectively. During peak hour, the VITM model yields a total of 4,253 in MMC and 5,519 in RMH catchments. The Google Map model yields a total of 4,213 in MMC and 5,599 in RMH catchments. In this case and assuming 10% of the patients are eligible them the estimated number of cases are 425 for MMC and 552 for RMH (**Supplementary Table 3**).

DISCUSSION

The key finding from this study is that the travel time forecasts from the Google Maps API is similar to that obtained by a strategic transport model and that the two-hospital model comprising of RMH and MMC provided the optimal solution with respect to inter-peak traveling time into the future. We were able to explore future

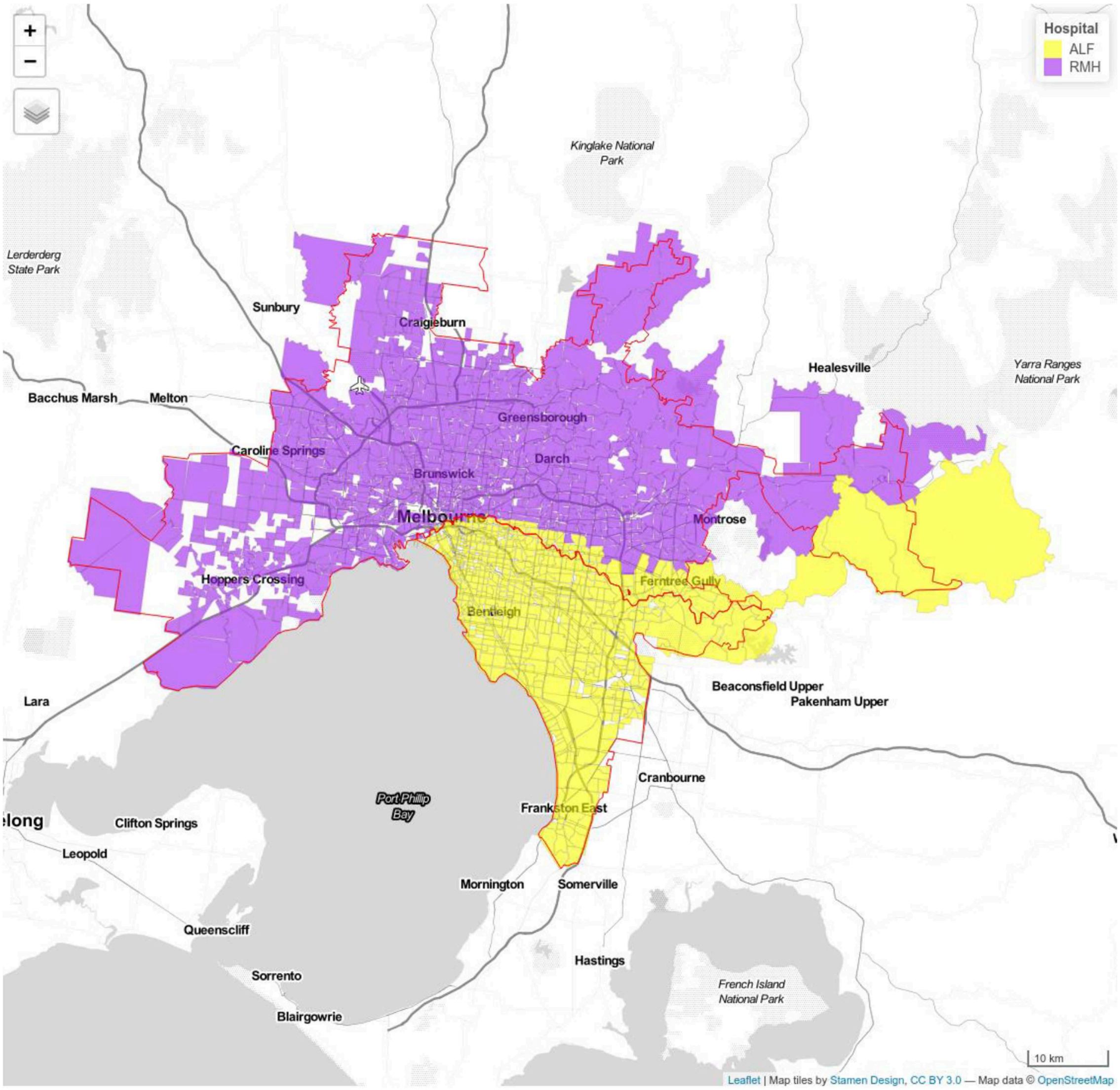

FIGURE 2 | Model 1b Royal Melbourne (RMH) and Alfred Hospitals (ALF). Royal Melbourne Hospital's catchment has purple color and Alfred Hospital catchment is displayed with yellow color.

transport scenarios up to 10 years and found that this combination remains stable suggesting the RMH and MMC combination is robust in both current and future scenarios. We propose that a combination of the two methods should be used to model hospital catchment for stroke or other medical illness.

Strategic Transport Model and the Google Maps API

The strategic transport model requires someone trained in its use and cannot be used easily by someone unfamiliar with the methodology. Running the model can take several weeks whereas the simulation with the Google Maps API can be performed overnight. Further, the license for the use of this model come from the Department of Transport and thus it is not open for public access. By contrast, the Google Maps API is open to the public upon signing up at the Google Developers' website. The two methods differ in that the main objective of strategic transport demand models is to meet long-term mobility needs on the basis of socio-economic scenario and land-use characteristics (25). As such strategic transport models like VITM produce transport metrics at the aggregate level of zone called traffic analysis zone. By contrast, the Google Maps API estimates travel time for a given trip at the specified time to individual addresses within zones. A critical difference between a strategic transport model and the Google Maps API is that the strategic transport model can be used for future travel planning. We were reassured our findings with the Google Maps API were confirmed with the strategic model using the high value on Nash-Sutcliff of model efficiency.

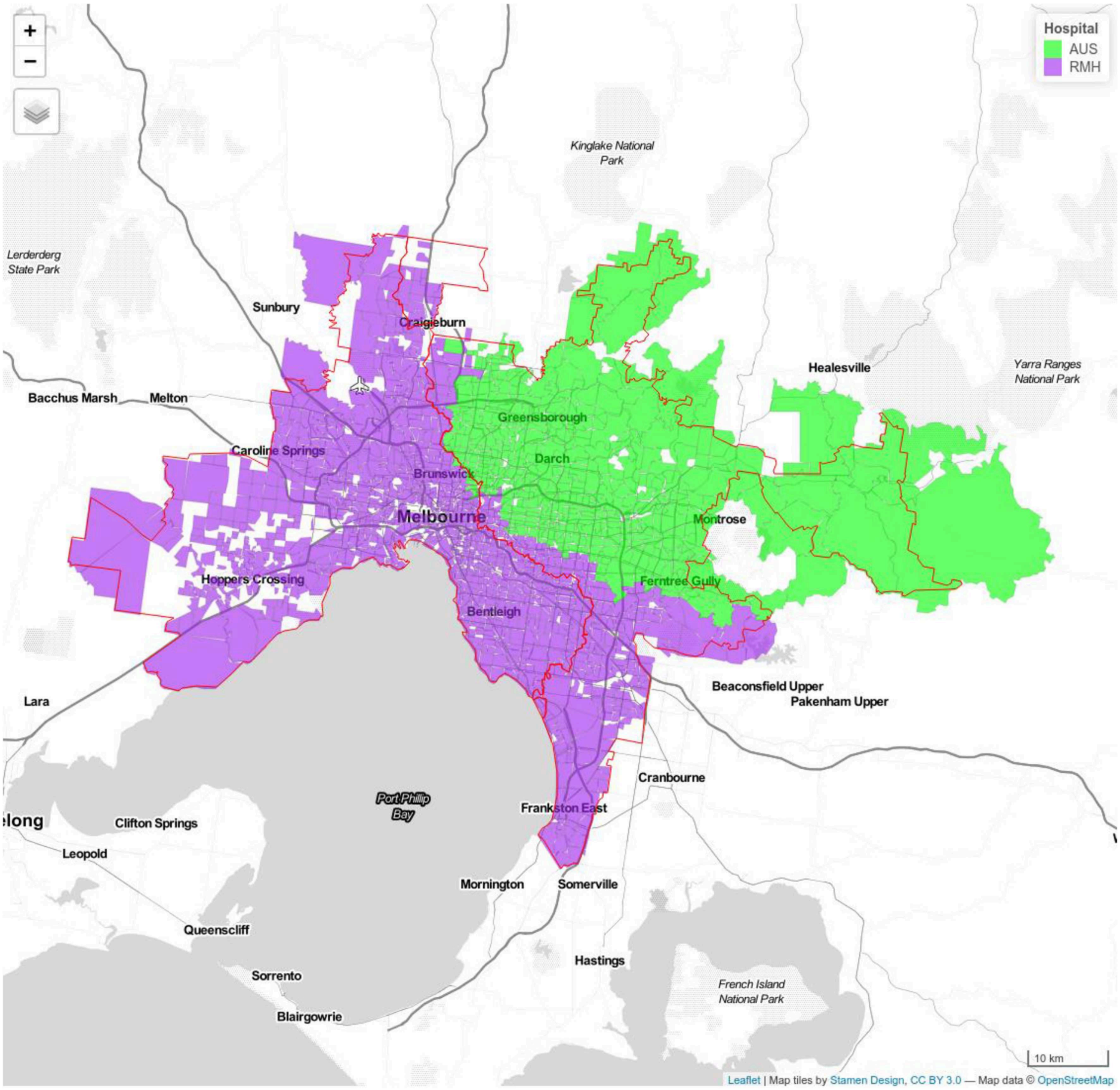

FIGURE 3 | Model 1c Royal Melbourne (RMH) and Austin Hospitals (AUS). Royal Melbourne Hospital's catchment has purple color and Austin Hospital's catchment is displayed with green color.

Strategic Transport Model in Australia and Around the World

Similar research can be conducted for other cities. For example, in Adelaide the MASTEM (The Metropolitan Adelaide Strategic Transport Evaluation Model) (26) and the STM (The Strategic Travel Model) in Sydney can be used in a same way to define the ECR service boundaries in this City (27). In England, the London Transport Studies (LTS) (28) is available while in Zurich and Singapore, an agent based (MATsim) model is available (29).

Our study has several limitations. The focus in this paper and our earlier paper has been on travel time (18). These are other issues to consider such as the government willingness to pay and the allocated budget, the number of available accredited interventional neuroradiologists and stroke (vascular) neurologists and the observed number of stroke cases requiring ECR. For example, the requirements to apply for second designated ECR hub in Victoria included sufficient number of accredited interventional neuroradiologists (4 at MMC) and stroke neurologists (5 at MMC) and 2 angiographic suites. A coalition of 2 ECR hubs would be able to handle 4 cases simultaneously every 2 h. Such a scenario has not yet been reached. The use of VITM for predicting future scenarios are based on a number of inputs to the model and as these scenarios are estimate of future events. In this study, the term "stable" has been used to describe the lack of variation in the catchment over the years for the combination of RMH and MMC. It was 6% change in the peak traffic model for this combination and 8% decrement for the RMH and ALF and 7% decrement for RMH and AUS.

The current study does not address the issue of model of patient care such as treatment at "mothership" or treat at the local hospital first, so called "drip and ship" (8, 9). There are various arguments either way. Proponents of treatment with "direct to mothership" model would point to the better outcome with direct transfer, possibly from avoiding delay from inter-hospital transfer and earlier revascularization (10, 11). A cautious approach would be to evaluate the capacity of the "mothership" hospital to handle the diversion of all patients to the mothership before imaging. Using very conservative estimate of 10% eligible patients, the "mothership" hospital would face a deluge of patients to process to treat in order to perform ECR on 434 patients at MMC or 543 patients at RMH. A variety of tools are now available to screen patients for LVO (30, 31). However, a formal prospective field testing of these tools and the impact on hospital case load has not yet been evaluated. Prior study had suggested that evaluation of models of care should include different type of hospital ability and ambulance transport (7). We would add the use of screen tool for LVO in the modeling approach.

CONCLUSION

In summary, we introduced a trip-based demand model to estimate the catchment area for ECR hubs and assess the stability of the model over time. This method can be applied in designing and planning ECR services not only in different states of Australia but also in Metropolitan cities over the world.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

TP, RB, and HV: design. AT, HV, and RB: analysis. TP, HV, RB, GC, HM, and VS: writing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00692/full#supplementary-material

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ORIGINAL RESEARCH
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Pre-hospital Triage of Acute Ischemic Stroke Patients—Importance of Considering More Than Two Transport Options

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Background: Patients with acute ischemic stroke (AIS) and large vessel occlusion benefit from rapid access to mechanical thrombectomy in addition to intravenous thrombolysis. Prehospital triage algorithms to determine the optimal transport destination for AIS patients with unknown vessel status have so far only considered two alternatives: the nearest comprehensive (CSC) and the nearest primary stroke center (PSC).

Objective: This study explores the importance of considering a larger number of PSCs during pre-hospital triage of AIS patients.

Methods: Analysis was performed in random two-dimensional abstract geographic stroke care infrastructure environments and two models based on real-world geographic scenarios. Transport times to CSCs and PSCs were calculated to define sub-regions with specific triage properties. Possible transport destinations included the nearest CSC, the nearest PSC, and any of the remaining PSCs that are not closest to the scene, but transport to which would imply a shorter total time-to-CSC-via-PSC.

Results: In abstract geographic environments, the median relative size of the sub-region where a triage decision is required ranged from 34 to 92%. The median relative size of the sub-region where more than two triage options need to be considered ranged from 0 to 56%. The achievable reduction in time-to-thrombectomy ("benefit") exceeded the increase in time-to-thrombolysis ("harm") by a factor of 2 in 30.5–37.0% of the sub-region where more than two triage options need to be considered. Results were confirmed in geographic environments based on real-world urban and rural stroke care infrastructures.

Conclusion: Pre-hospital triage algorithms for AIS patients that only take into account the nearest CSC and the nearest PSC as transport destinations may be unable to identify the optimal transport destination for a significant proportion of patients.

Keywords: pre-hospital triage, decision analysis, ischemic stroke, thrombolysis, mechanical thrombectomy, health services research, geospatial modeling, mathematical modeling (medical)

INTRODUCTION

Background

International guidelines recommend early administration of intravenous thrombolysis for eligible patients with acute ischemic stroke (AIS); in addition, patients with proximal large vessel occlusion (LVO) should receive mechanical thrombectomy (MT) as quickly as possible (1). As the clinical benefit of both thrombolysis (2–4) and MT (5–7) diminishes over time, research efforts in recent years have focused on improving clinical outcome by reducing pre-hospital (8–10) and intra-hospital delays (11, 12). With regard to pre-hospital delays, directly transporting AIS patients to an MT-capable comprehensive stroke center (CSC) instead of a nearer non-MT-capable primary stroke center (PSC) has been suggested as one strategy to reduce time to MT for patients with LVO (13). Given that information about the vessel status of patients is typically not available to emergency medical personnel in the field, patients that are likely to benefit from direct transportation to a CSC need to be selected based on clinical and demographic variables. Several clinical pre-hospital stroke severity scales with similar accuracies to estimate the likelihood of LVO exist (14); however, the optimal instruments as well as the most appropriate cutoff values to inform pre-hospital triage decisions and to select patients for direct transportation to a CSC are not currently known (1). Previous studies that explored the impact of triage algorithms to determine the most adequate transport destination for AIS patients only allowed for a decision between two alternatives, namely transport to the nearest CSC, bypassing all PSCs; and transport to the nearest PSC (15–17). However, clinical experience as well as fundamental geographic observations suggest that oftentimes a PSC that is not nearest to the scene, but from which a patient could be transferred quickly to a CSC if necessary, might be a better primary transport destination option than the nearest PSC.

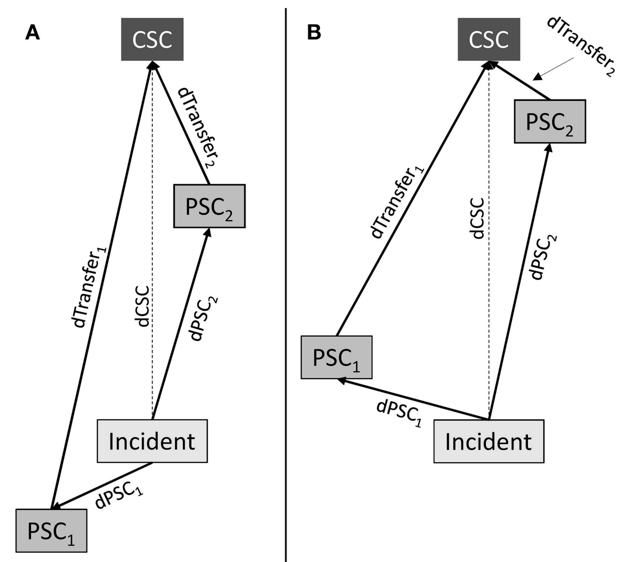
Objective

In the current study, we aimed to evaluate the importance of considering all possible transport destinations during pre-hospital triage of AIS patients beyond the established "directly to CSC vs. nearest PSC" paradigm.

METHODS

Model

The importance of extending the array of possible transport destinations was explored in abstract two-dimensional geographic stroke care environments and subsequently in two different real-world geographies. For the first part of the analysis, we used computational simulations to generate independent random realizations of abstract geographic environments characterized by different numbers of PSCs (2–10) and CSCs (1–4) that could be reached within established treatment time windows. The range of the number of stroke centers was chosen to reflect different stroke care infrastructure environments while considering computational efficiency. PSCs were assumed to be comparable in terms of door-to-needle and door-in-door-out time. Locations of stroke centers were determined by a homogenous spatial Poisson



dCSC:	43 min
$dPSC_1$:	13 min
$dPSC_2$:	24 min
$dTransfer_1$:	55 min
$dTransfer_2$:	16 min

dCSC:	43 min
$dPSC_1$:	19 min
$dPSC_2$:	34 min
$dTransfer_1$:	38 min
$dTransfer_2$:	9 min

FIGURE 1 | Higher order triage with three potential transport destinations. Abstract geographic scenarios with one comprehensive (CSC) and two primary stroke centers (PSC). Lengths of arrows displayed in the table at the bottom represent driving time. Transport time from the location of the stroke incident to the CSC is larger than to any one of the two PSCs. Additionally, primary transport to the nearest PSC (PSC_1) is associated with longer transport time to the CSC for patients requiring secondary transfer as compared to primary transport to PSC_2. The benefit/harm ratios (BHR) associated with considering PSCs that are not nearest to the scene (in this example: PSC_2) can be calculated (1) in relation to the patient being transported to the nearest PSC; and (2) in relation to the patient being transported directly to the nearest CSC. For (1), it is the ratio of the reduction in time-to-MT and the increase in time-to-thrombolysis; for (2), the ratio of the reduction in time-to-thrombolysis and the increase in time-to-MT:

$$BHR_{PSC} = \frac{(dPSC_1 + dTransfer_1) - (dPSC_2 + dTransfer_2)}{dPSC_2 - dPSC_1}.$$

$$BHR_{CSC} = \frac{dCSC - dPSC_2}{(dPSC_2 + DIDO + dTransfer_2) - dCSC}.$$

(A): Nearest PSC (PSC_1) and CSC are in opposite directions from the scene while another PSC that is not nearest to the scene (PSC_2) lies in direction toward the CSC:

$$BHR_{PSC} = \frac{(13 + 55) - (24 + 16)}{24 - 13} = 2.54,$$

$$BHR_{CSC} = \frac{43 - 24}{(24 + 60 + 16) - 43} = 0.33.$$

(B): Both PSCs lie in direction toward the CSC:

$$BHR_{PSC} = \frac{(19 + 38) - (34 + 9)}{34 - 19} = 0.93,$$

$$BHR_{CSC} = \frac{43 - 34}{(34 + 60 + 9) - 43} = 0.15.$$

point process in the disc. The base unit of the model was taken as driving time under current weather and traffic condition which were assumed homogenous within the incident region. To explore the impact of different spatial stroke center densities, two models with different radius of the disc (30 and 120 min) were analyzed separately. The travel time from any point within the incident region to any CSC or PSC was calculated as the Euclidean distance between the two locations.

For the second part of the analysis, real-world geographic scenarios with stroke center distributions and traffic network infrastructures based on those of Berlin, Germany (metropolitan region) and those of Brandenburg, Germany (mixed rural region) were used. Since an unusually high proportion of stroke centers in the city of Berlin offer MT-services (up to 11 of 14, depending on the time of day), we limited the availability of MT-services in the analysis of the urban scenario to three university hospitals (see **Supplementary Data** for a detailed description of the two regions). Distances between points were determined with the haversine formula and transformed into driving times using the Google Maps Distance Matrix API.

Definition of Sub-regions and Benefit/Harm Ratio

For all scenarios, sub-regions were defined according to specific patterns of travel times from the points within the sub-region to the CSCs and PSCs. All locations at which the closest stroke center was a CSC and thus only one reasonable transport destination exists were defined as unconditional catchment regions of a CSC. We defined the triage region as all points where the nearest stroke center was not a CSC. This region was further sub-divided according to the number of transport destinations that need to be considered for an exhaustive triage decision. Potential transport destinations included the nearest CSC, the nearest PSC, and, in addition, any of the remaining PSCs that are not closest to the scene, but transport to which would imply a shorter total time-to-CSC-via-PSC as compared to transport to any other PSC that is closer to the scene. The higher order triage region was defined as all points where more than two possible transport destination existed (see **Supplementary Data** for formal mathematical definitions).

To quantify the potential clinical usefulness of considering additional PSCs as primary transport destinations, for each point within the higher order triage region, we calculated two types of

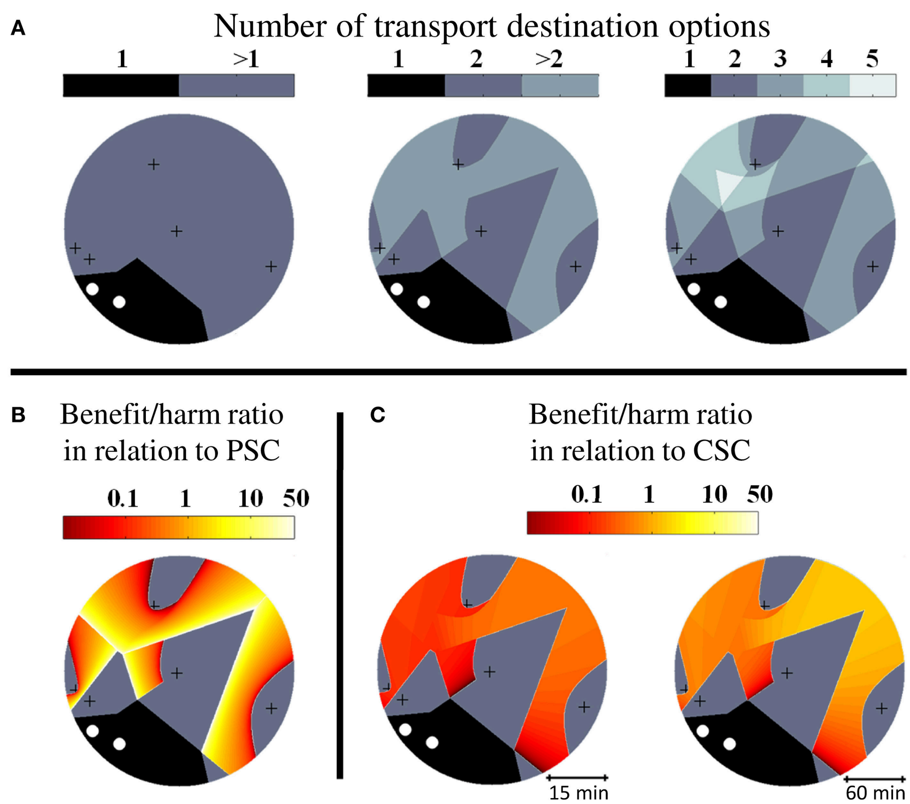


FIGURE 2 | Higher order triage in abstract geographic environments. Visualization of triage sub-regions and benefit/harm ratios in exemplary abstract geographic scenarios with two comprehensive stroke centers (CSC, white circles) and five primary stroke centers (PSC, black crosses). **(A):** Diagram on the left shows the extent of the unconditional catchment region of the CSCs (1) and the extent of the region where more than one possible transport destination exist and hence a triage decision is required (>1). The diagram in the middle highlights the sub-region where more than two triage options need to be considered (>2). The diagram on the right shows the subdivision of the higher order triage region according to the number of transport destination options (3–5). **(B):** Spatial distribution of the benefit/harm ratio in relation to the nearest PSC. **(C):** Spatial distribution of the benefit/harm ratio in relation to the nearest CSC.

ratios: (1) the ratio of the reduction in time-to-MT ("benefit") and the increase in time-to-thrombolysis ("harm") associated with primary transport to each additionally considered PSC as compared to primary transport to the nearest PSC. And (2) the ratio of the reduction in time-to-thrombolysis ("benefit") and the increase in time-to-MT ("harm") associated with primary transport to each additionally considered PSC as compared to primary transport to the nearest CSC. The greatest of the ratios between the so determined benefits and harms for each point within the higher order triage region was defined as surrogate parameter of the potential clinical usefulness of considering additional PSCs (**Figure 1**). Calculation of the benefit/harm ratio in relation to the nearest CSC required specification of a door in-door out time, which was assumed to be 60 min and varied in sensitivity analyses.

Analysis

For the statistical analysis of abstract geographic scenarios, 50 random geographic stroke care environments were simulated for each combination of PSCs and CSCs. Results are presented as full distributions or as summary statistics with boxplots showing the median and interquartile ranges (IQR). All simulations and analyses were performed in MATLAB (18).

No ethical approval and no informed consent was required for this study. The MATLAB code of our project is publicly available on GitHub (https://github.com/lschlemm/Higher-Order-Effects-of-Prehospital-Triage).

RESULTS

Random Scenarios

In a first step, we created random geographic stroke care environments with different numbers of CSCs and PSCs and determined the regions with characteristic properties relating to pre-hospital triage decisions. An exemplary geographic setting with two CSCs and five PSCs together with graphical illustrations of the size and distribution of the sub-regions and the benefit/harm ratios is shown in **Figures 2A–C**. In geographic settings with two CSCs and five PSCs, the median benefit/harm ratio calculated in relation to the nearest PSC was 1.02 (IQR 0.81–1.11). Since transportation of a patient to a PSC instead of a CSC involves an additional secondary transfer, the median benefit/harm ratio calculated in relation to the nearest CSC was lower than the benefit/harm ratio calculated in relation to the nearest PSC and depended on the average driving time between stroke centers (incident region with a radius of 30 min: median 0.13, IQR 0.09–0.18; incident region with a diameter of 120 min: median 0.56, IQR 0.35–0.77).

Identical calculations to those presented for stroke care infrastructure environments with two CSCs and five PSCs were performed for all combinations of different numbers of CSC: 1–4 and numbers of PSC: 2–10. The relative size of the triage region where a triage decision is required and the relative size of the higher order triage region where more than two triage options need to be considered depended on both the total number of CSCs and the total number of PSCs with medians ranging from 34 to 92% and 0 to 56%, respectively. The relative sizes of both

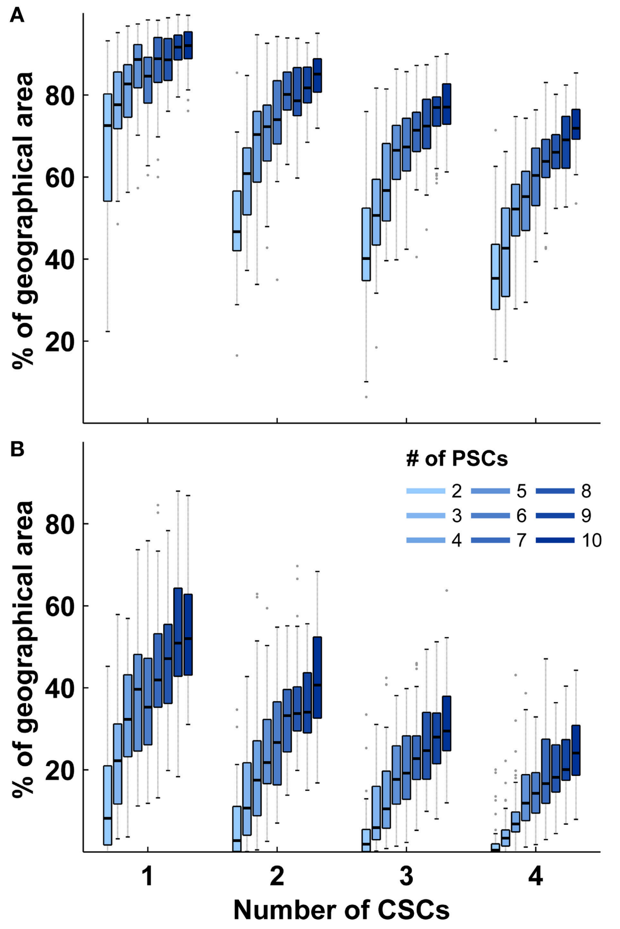


FIGURE 3 | Relative sizes of triage sub-regions in abstract geographic environments. **(A):** Distribution of the relative size of region where a triage decision is required in relation to the total size of the geographic region according to the number of comprehensive and primary stroke centers. **(B):** Distribution of the relative size of region where more than two transport destinations need to be considered in relation to the total size of the geographic region according to the number of comprehensive and primary stroke centers. Shown are the median and interquartile ranges (IQR); length of whiskers correspond to 1.5-times the IQR. PSCs indicates primary stroke center; CSC, comprehensive stroke center.

regions showed a negative correlation with the total number of CSCs and a positive non-linear association with the total number of PSCs (**Figure 3**). Across all geographic scenarios, the median of the benefit/harm ratio calculated in relation to the nearest PSC was 1.01 (IQR 0.84–1.19) with slightly higher values in geographic scenarios with fewer PSCs (**Figure 4A**). The reduction in time-to-MT exceeded the increase in time-to-thrombolysis by a factor of at least 2 in 30.5–37.0% of the area of the higher order triage region As expected, the benefit/harm ratio calculated in relation to the nearest CSC was lower (incident region with a radius of 30 min: median 0.13, IQR 0.08–0.20; incident region with a radius of 120 min: median 0.41, IQR 0.25–0.67) with slightly higher values in geographic scenarios with more PSCs (**Figures 4B,C**). Similar results were obtained assuming a door in-door-out time of 30 and 90 min.

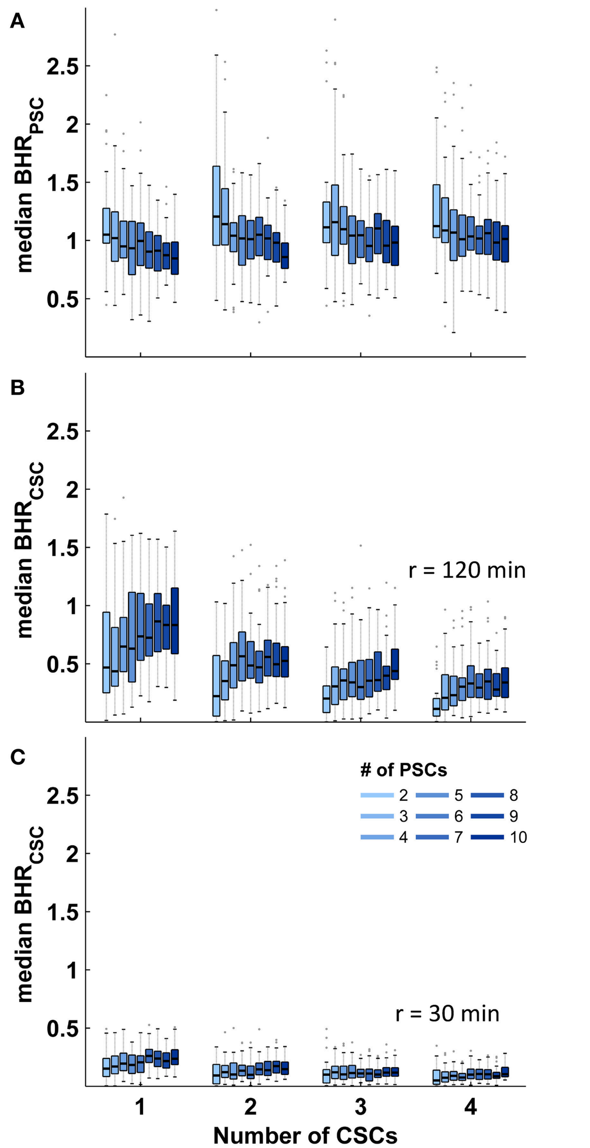


FIGURE 4 | Benefit/harm ratios in abstract geographic environments. Distribution of the spatial median of the benefit/harm ratios (BHR) in regions where more than two transport destinations need to be considered according to the number of primary (PSCs) and comprehensive stroke centers (CSCs). **(A):** Benefit/harm ratio in relation to the nearest PSC. **(B,C):** Benefit/harm ratio in relation to the nearest CSC. Shown are the median and interquartile ranges (IQR); length of whiskers correspond to 1.5-times the IQR.

Real World Scenarios

To confirm validity of the results obtained in abstract geographic environments, analyses were also performed in two scenarios based on the geographic stroke care infrastructure environments of Berlin (urban) and Brandenburg (rural). In the urban environment, the relative size of the triage region where a triage decision is required and the relative size of the higher order triage region where more than two triage options need to be considered were 84% and 35%, respectively. In the rural environment, relative sizes were 81% and 52%, respectively (**Figure 5A**). The order of magnitude and distribution of the benefit/harm ratios calculated in both real-world environments were comparable to those obtained in abstract geographic scenarios: the median benefit/harm ratios in relation to the nearest PSC in the urban and rural environment were 0.39 (IQR 0.10–1.92) and 0.57 (IQR 0.29–1.22), respectively. The reduction in time-to-MT exceeded the increase in time-to-thrombolysis by a factor of at least 2 in 21% of the area of the higher order triage region in the urban environment and in 12.9% in the rural environment. The benefit/harm ratios in relation to the nearest CSC were overall small, and lower in the urban environment (median 0.10. IQR 0.08–0.18) than in the rural environment (median 0.14. IQR 0.09–0.20), reflecting a greater influence of the door in-door out time in relation to transport times (**Figures 5B,C**).

DISCUSSION

Main Findings

We analyzed the importance of considering all possible transport destinations during pre-hospital triage of AIS patients in abstract and real-world geographic stroke care environments. Our results suggest that more than two possible primary transport destinations exist for a significant proportion of geographic locations. At approximately one third of those, the reduction in time-to-MT associated with direct transportation of a patient to a PSC that is not nearest to the scene is at least twice as large as the increase in time-to-thrombolysis. As expected, the relative size of the sub-region where more than two triage options need to be considered depends on the number of PSCs and CSCs and is largest for environments with few CSCs and many PSCs.

Previous Studies

To the best of our knowledge, no previous study has explored the impact of extending the array of stroke centers considered as primary transport destinations in pre-hospital triage algorithms beyond the established "directly to CSC vs. nearest PSC" paradigm. Increasingly, pre-hospital clinical stroke severity scales are being investigated as tools to identify patients with LVO that might benefit from direct transportation to a CSC (14); however, there is currently not enough evidence to recommend use of one specific scale in clinical practice (1). The results of our analysis have direct implications for the concept of pre-hospital triage of patients with suspected AIS: When the number of possible transport destinations exceeds two, decision support algorithms with a binary response, such as a fixed cutoff value of pre-hospital clinical stroke severity scales, are unsuitable for informing pre-hospital triage decisions. Instead, it is necessary to estimate the clinical outcome of individual patients given a set of clinical predictor variables, i.e., age, sex, comorbidities, and stroke severity (the latter operationalized by one of the available pre-hospital scales); the post-test probability of the presence of MT-treatable LVO; and the estimated delays to the initiation of thrombolysis and—if indicated—MT associated with each transport destination. It has previously been shown that estimation of clinical outcome parameters with conditional probabilistic models can be used to guide decisions regarding the optimal transport destination for AIS

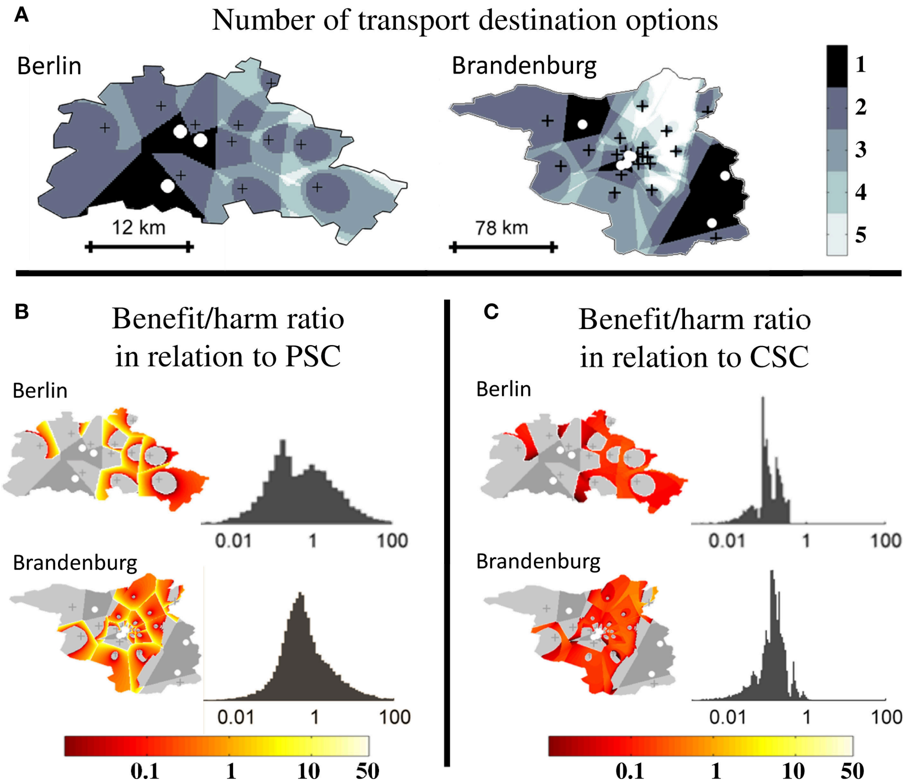


FIGURE 5 | Higher order triage in real-world geographic scenarios. Extent of triage sub-regions and benefit/harm ratios in a real-world urban (Berlin) and rural (Brandenburg) geography. Comprehensive stroke centers (CSC) are marked with white circles and primary stroke centers (PSC) with black crosses. **(A):** Regional subdivision according to the number of transport destination options. **(B):** Spatial distribution and frequency distribution of the benefit/harm ratio in relation to the nearest PSC. **(C):** Spatial distribution and frequency distribution of the benefit/harm ratio in relation to the nearest CSC.

patients (16, 19). In addition, a proof-of-concept study involving abstract geographic scenarios with one single CSC and PSC demonstrated that use of variable clinical stroke severity scale-derived cut-offs values that take into account estimated transport times may lead to better clinical outcomes than fixed cutoff values (20).

Clinical Implications

Not all patients suffering an ischemic stroke at a geographic location where more than two transport destinations exist would equally benefit from an exhaustive triage strategy: Patients with a low probability of LVO would only be expected to benefit at locations where the benefit/harm ratio in relation to the nearest PSC is high, while patients with more severe stroke symptoms and a higher probability of LVO would be expected to also derive benefit at locations with a lower benefit/harm ratio. Using the numerical values for the reduction in disability-adjusted life days per minute faster treatment published by Meretoja et al. (3, 7), the cut-off values for the benefit/harm ratio, above which a patient is expected to benefit from the consideration of higher order triage options, can be calculated as $\frac{1-pLVO}{pLVO} \times \frac{Effect_{Thrombolysis}}{Effect_{Thrombectomy}}$. For an estimated probability of LVO of 10, 30, and 50%, the cutoff values are 3.9, 1, and 0.4, respectively. Importantly, these cutoff values only apply if the patient would not be transferred directly to the nearest CSC in the first place.

In clinical practice, pre-hospital triage algorithms to determine the best transport destination for patients with suspected AIS are only needed if patients are eligible for both thrombolysis and MT. In addition, since no data are currently available regarding the impact of different triage destinations on the outcome of patients with stroke mimics and hemorrhagic strokes, decisions for patients with *suspected* AIS have to be made based on the expected outcome of patients with *definite* AIS. Accordingly, in our analysis, we focused on patients with definite AIS who, after careful assessment of indications and contraindications, would fulfill the eligibility criteria for both thrombolysis and MT. In future studies modeling the impact of pre-hospital triage strategies, if would be desirable to include data on the clinical outcome of patients with other diagnoses than AIS, such as hemorrhagic stroke, as a function of pre-hospital delay and type of hospital (PSC or CSC). Currently, however, such data are not available.

Depending on specific geographic circumstances and the relative locations of stroke centers to each other, implementation of pre-hospital triage algorithms can lead to a shift of AIS patients from PSCs to CSCs. In addition, triage algorithms that consider all potential transport destination options can also lead to increased number of AIS patients at certain PSCs. How these changes in the distribution of patient volumes affect quality of care in the short, medium, and long term (e.g., decrease due to reduction of experience at PSCs, or due to insufficient resources to cope with additional workload) was not addressed in the current study.

Limitations

We are aware of the following limitations regarding the findings of our study. First, we assumed similar door-to-needle and door-in-door-out times across all PSCs. When using pre-hospital triage algorithms in clinical practice, best estimates for PSC-specific treatment time metrics derived from recent historical data collected at each PSC should be used. In addition, in the base-case scenario, a door in-door-out time of 60 min was used, which is shorter than what is currently observed in high-volume centers (21, 22). We decided to assume a shorter median door in-door out time to be able to investigate the effect of considering all potential transport destination options during pre-hospital triage in a health care system in which other modifiable factors contributing to treatment delay have been addressed. When a door in-door-out time of 30 and 90 min was assumed in univariate sensitivity analyses, results were similar to the base case scenario. In general, longer door in-door out times would leave the relative sizes of the triage sub-region as well as the benefit/harm ratio calculated in relation to the nearest PSC unaffected, and decrease the benefit/harm ratio calculated in relation to the nearest CSC. Second, part of the results were based on abstract geographical models in the two-dimensional plane; in such models involving a total number of points less than or equal to three, the distance between two points can be modeled to directly reflect the transport times between these two points. Since the determination of sub-regions and the calculation of potential clinical usefulness in our model involved comparison of distances between more than three points, our model requires the assumption of proportionality between geographic distances and transport times, i.e., the assumption of one single mode of transport and an overall homogenous quality of the transport infrastructure within the modeled area (e.g., roads, weather conditions). Our findings cannot be used to determine the optimal transport destination for a given patient; instead the results of our study indicate that consideration of more than two transport destinations may often be needed for an exhaustive pre-hospital triage decision. Due to the theoretical nature of this study, confirmation of the accuracy of our results in clinical settings is required.

Conclusion

In conclusion, our results suggest that for a non-negligible number of AIS patients, more than two possible transport destinations exist and should be considered in pre-hospital triage algorithms. Depending on geographic circumstances and stroke severity, patients may have better clinical outcome when transported primarily to a PSC that is not closest to the location of the incident. Future studies should aim to develop and validate pre-hospital triage algorithms that predict clinical outcome based on patient-specific clinical data and that include stroke centers beyond the nearest CSC and the nearest PSC when determining the optimal transport destination for AIS patients.

AUTHOR CONTRIBUTIONS

LS and ES jointly conceived the study. LS reviewed the literature, developed the model, performed the simulations, analyzed and interpreted the data, and wrote the first draft of the manuscript. ES performed preliminary simulations and confirmed integrity of the final model. All authors reviewed and edited the manuscript for intellectual content and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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ORIGINAL RESEARCH
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Testing the Usability of a Software for Geospatial and Transport Modeling in Acute Stroke Service Planning

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Introduction: Geographic visualizations have been used to understand disease since the nineteenth century. We developed a software that creates simple visualizations which can be used as a decision support tool for pre-hospital acute stroke transportation planning. In this study, we test the usability of this software to improve user experience and assess the interpretability of the visualizations it produces as it relates to planning and optimizing stroke systems of care.

Materials and Methods: Healthcare practitioners and administrators working within the acute stroke system in Alberta, Canada were invited to participate. Participants were randomized to either the geographic visualization or 2-D temporospatial diagrams. Using a standardized script participants were asked to complete tasks and interpret the visualizations produced by the software. The computer screen and audio were recorded. Recordings were transcribed verbatim and analyzed using inductive thematic analyses. The number of errors made and time to task completion were also analyzed.

Results: Eighteen participants (8 physicians, 5 healthcare administrators, 3 paramedics, and 2 nurses) were enrolled. Mean age was 41.22 years (SD: 10.55) and 8 participants were female. It took users a mean of 1.59 min (SD: 0.71) to complete all 10 tasks for the geographic visualizations and a mean of 1.08 min (SD: 0.33) to complete all 15 tasks for the 2-D temporospatial diagrams. Map users made a median of 2 errors (IQR: 4), 2-D temporospatial diagram users also made a median of 2 errors (IQR: 1.5). All but one map user correctly interpreted all maps, only three of the eight 2-D temporospatial diagram correctly interpreted all diagrams. In the qualitative analysis three common themes were identified: comments on the user interface, comments on the visualization tool(s), and suggestions for improvement. Most study participants mentioned that the software would be useful in their work.

Conclusions: Healthcare professional from several different aspects of stroke care see geographic visualizations in transport decision making to be a useful tool. The software demonstrated high usability. However, several suggestions were made to improve user experience as well as additional features which could be developed and become the subject of future studies.

Keywords: geographic visualizations, acute stroke, software, patient transport, health services research

INTRODUCTION

The use of geographic visualizations to better understand disease dates back to Dr. John Snow's seminal studies of cholera outbreak in London in the nineteenth century (1). Geographic and spatial visualizations continue to be used today, classically in infectious disease epidemiology to track disease burden in the population, assess patterns of disease transmission, and predict or manage disease outbreaks (2–8). However, geographic visualizations can now be found in cancer epidemiology (9), the planning of emergency room and neonatal intensive care unit locations (10, 11), as well as analyzing equity in access to healthcare services (12–14).

The consideration of geography is especially timely and important in stroke care right now. The complex pre-hospital decision making required for optimal transportation of acute ischemic stroke patients with suspected large vessel occlusion (LVO) lends itself well to geographic visualizations and analyses. For patients with acute ischemic stroke due to suspected LVO endovascular therapy (EVT) was recently proven both more effective than and synergistic with alteplase (15–19). However, EVT is typically only available at large urban hospitals (herein referred to as EVT centers) while alteplase is more widely available at EVT centers and at smaller community hospitals (herein referred to as thrombolysis centers). There are two transport options available to these patients: (1) direct transport to an EVT center for alteplase and/or EVT, which may entail bypassing closer thrombolysis centers (mothership transport); or (2) transport to a thrombolysis center for alteplase first and then transfer to an EVT center for EVT (drip-and-ship transport). Given the geographic disparity in treatment availability and the highly time-sensitive nature of both treatments the optimal transport method is often unknown.

Previously, a conditional probability model which determines the best transport option (drip-and-ship or mothership) based on predicted patient outcomes has been developed (20). Due to the complexity of the model a simple geographic visualization was needed to clearly display its results. A cloud-based software application [DEcision Support Tool IN Endovascular therapy (DESTINE)] was developed to display the models results visually (21). The software is customizable to a given region's unique circumstances (location of treatment centers, treatment efficiency, and field population). The software can generate maps of specific geographies (see example in **Figure 1**) or generalized figures (2-dimensional temporospatial diagrams) for a non-specific regions (see example in **Figure 2**) which depict the best transport decision for patients.

As the use of geography in clinical decision making grows there is a need to develop easy to use software programs to convey this information both quickly and simply to decision makers. It is important that in parallel with the development of decision support tools their usability be tested. The purpose of performing usability studies is to ensure that products are easy to learn, effective to use, and users have a positive experience with the product (22). Usability study can involve several different methodologies. Here we employ feature inspection to assess usability which is the assessment of sequences to accomplish a particular task. In performing feature inspection one checks for long or unnatural sequences or steps which would require extensive experience with the product to perform (23). In this study we use feature inspection to assess the speed and ease of software use and identify any areas for improvement. As the 2-D temporospatial diagrams are a novel visualization technique and the use of maps visualizations as a decision support tool for stroke transportation is also new we also aimed to assess the interpretability of these visualizations in planning and optimizing stroke systems of care.

MATERIALS AND METHODS

Participants

Healthcare practitioners and administrators working within the acute stroke system in Alberta, Canada were invited to participate. Users from all aspects of acute stroke care spanning emergency medical services, to in-patient physicians to stroke system planners were invited to ensure a variety of perspectives were obtained.

Usability Testing

Participants were randomized to either the geographic visualization of the province of Alberta, Canada or the 2-D temporospatial diagram. The participants were advised only that the usability of the software was being assessed, not their individual abilities. During the usability test, participants were provided with access to the software and given specific task to perform to generate visualizations. An example of a task would be: "For the map on the right, change the Door-to-Needle time at the thrombolysis center to 70 min." The participants were then asked to interpret these visualizations (example: "In the town of Stettler, which is located just East of Red Deer, which transport option predicts the best outcome for the average patient in this scenario?") and finally were asked several open-ended questions to garner their qualitative feedback on their user experience (example: "What additional features, if any,

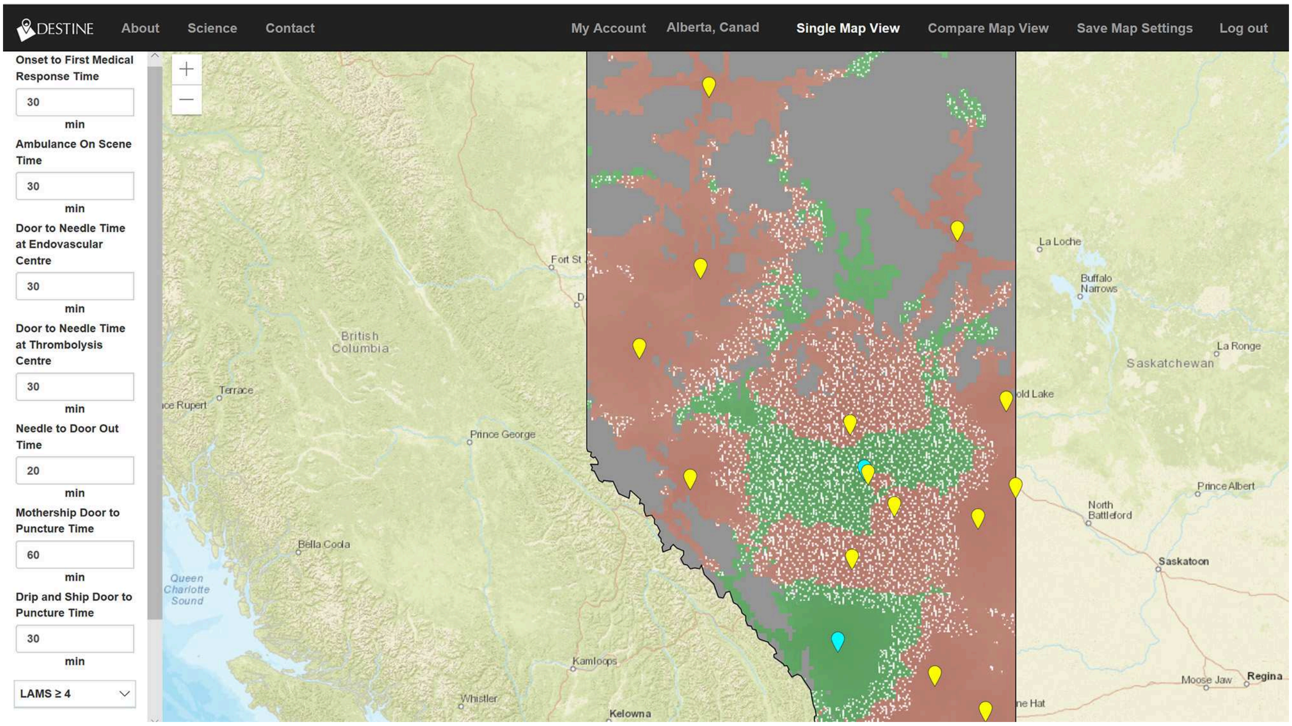

FIGURE 1 | Generated map from the DESTINE software (v0.01) showing Alberta, which was used in the usability tests. The user data entry panel is shown on the left-hand side. The top bar contains clickable items allowing the user to select the region of interest as well as convert from single map view to the compare map view. The resultant map visualization is displayed in the middle of the screen. The maps display endovascular therapy centers as blue icons and thrombolysis centers as yellow icons. The maps are color coded such that areas in red indicate that drip-and-ship predicts best patient outcomes, areas in green indicate mothership predicts best outcomes, and areas overlaid with white stippling indicate the difference in probability of good outcome between the two options is minimal (<0.01).

would you like to see?"). During the study, both the computer screen and room audio were recorded. A script was used by the researcher to ensure that each participant received the same instructions (see **Supplemental File 1** for full script with all tasks and interpretation questions).

Data Analysis

Each video and audio recording was analyzed and time to task completion and number of errors made during task completion were recorded. An error during task completion was defined as any event that the user clicked on an incorrect part of the software that would not result in the successful completion of the task. Quantitative data were tabulated and summarized using means and standard deviations (SD) or medians and interquartile ranges (IQR). Relationships between number of errors made and task length was examined using Pearson's correlation coefficient. All quantitative analyses were performed using Stata version 15.1 (Stata Corp. College Station, TX). Participant's answers to the questions regarding visualization interpretation and software user experience were transcribed verbatim by the researchers. Transcripts were read and analyzed using inductive thematic analyses. Common items were identified and organized into themes and subthemes. This process was iterated until no further themes/subthemes were identified and all comments were sorted. Qualitative data analyses were performed using Nvivo 12 (QSR International Ltd. Melbourne, AUS).

Ethics

This study was reviewed and approved by the Conjoint Health Research Ethics Board at the University of Calgary.

RESULTS

Participant Characteristics

The study enrolled 18 participants of whom 8 were physicians (including neurologists, fellows, and emergency room physicians), 5 were healthcare administrators (ranging from EMS administration to local hospital administration to provincial health network administration), 3 were paramedics, and 2 were nurses. The mean age of participants was 41.2 years (standard deviation 10.5 years) and 8 of participants were female. Participants self-reported a median computer proficiency score of 7 (IQR 1.75) on a 10-point scale with higher scores indicating better proficiency. Ten participants were randomized to evaluation of geographic visualizations of the province of Alberta, Canada; however, recording data from one of the participants was corrupted, so only data from nine participants were analyzed. Eight participants were randomized to evaluation of the 2-dimensional temporospatial diagrams. A breakdown

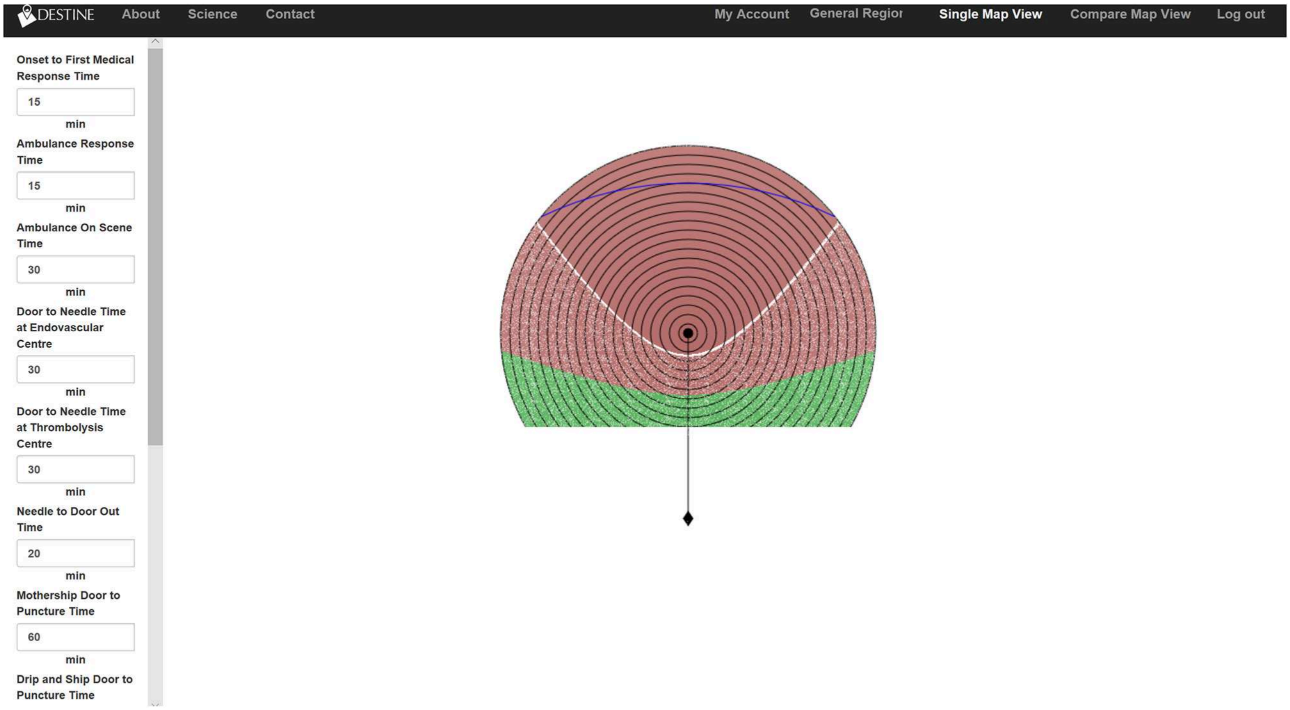

FIGURE 2 | Two-dimensional temporospatial diagrams from the DESTINE software (v0.01), which was used in the usability tests. The user data entry panel is shown on the left-hand side. The top bar contains clickable items allowing the user to select the region of interest as well as convert from single view to the compare view. The resultant temporospatial visualization is displayed in the middle of the screen. In the visualizations the thrombolysis center is represented by a black dot and the EVT center is represented by a black diamond below it. The travel time between the two centers is represented by the vertical line connecting them. The thrombolysis center is surrounded by concentric circles representing 5-min increments of travel time. The concentric circles only extend to the half-way point between the two centers as below this point the EVT center is the closest hospital to the patient and decision making would not be needed. The diagram is color coded such that areas in red indicate that drip-and-ship predicts best patient outcomes, areas in green indicate mothership predicts best outcomes and areas overlaid with white stippling indicate the difference in probability of good outcome between the two options is minimal (<0.01).

TABLE 1 | Participant characteristics.

Characteristic	Randomized to Alberta map visualization ($N = 10$)*	Randomized to 2-D temporospatial diagram ($N = 8$)
Mean age (SD)	41.10 (12.11)	41.38 (9.04)
Percent female (*N*)	30% (3)	62.5% (5)
Profession		
Physician (%)	40% (4)	50% (4)
Paramedic (%)	10% (1)	25% (2)
Health administrator (%)	40% (4)	12.5% (1)
Nurse (%)	10% (1)	12.5% (1)
Median self-reported computer proficiency (IQR)	7 (1.75)	7.5 (1.75)

**Includes demographic data from corrupted video recording.*

of participant characteristics by visualization randomized to is shown in **Table 1**.

Quantitative Task Performance for Geographic Visualization

Participants randomized to the geographic map visualization completed a total of 90 tasks. It took users a mean of 1.59 min (SD 0.71 min) to complete all 10 tasks. The maximum time it took a single user to complete all 10 tasks was 3.06 min. The mean time that it took users to complete each task was 9.51 s (SD: 8.05 s). The maximum time it took a single user to complete a single task was 112 s. The task that took the longest amount of time was selecting a LVO screening tool (mean: 28.33 s; SD: 33.47 s) followed by adjusting the transparency setting on the map (mean: 18.89 s; SD: 9.48 s).

Overall participants made very few errors during task completion (median: 2; IQR: 4); no participants completed all 10 tasks error free. Four of the tasks were completed error free by all participants. For the other six tasks >50% of participants completed each task error free and those who did make errors made a median of 1–2 errors per task. The maximum number of errors made by a single participant on a single task was 4 and the maximum number of errors made by a single participant across all tasks was 8. The two tasks which had the most errors made were selecting a screening tool (median: 2; IQR: 0.5; among participants who made errors) and adjusting the maps transparency (median: 2; IQR: 0.75; among participants who made errors). There was a positive correlation between mean number of errors made per task and mean length of time it took to complete the task ($r = 0.8373$, $p = 0.0025$).

Quantitative Task Performance for 2-Dimensional Temporospatial Diagrams

The users randomized to the 2-dimensional temporospatial diagrams completed 119 of 120 tasks in total; in one instance a software error occurred and the visualization was not generated, thus the following task could not be completed. It took users an average of 1.08 min (SD 0.33 min) to complete 15 tasks. The maximum time it took a single user to complete all 15 tasks was 1.77 min. The mean time that it took users to complete each task was 5.87 s (SD: 3.38 s). The maximum time it took a single user to complete a single task was 30 s. The task that took the longest amount of time was selecting a LVO screening tool (mean: 12.75 s; SD: 5.47 s).

Overall participants made very few errors during task completion (median: 2; IQR: 1.5); one participants completed all 15 tasks error free. Ten of the tasks were completed error free by all participants. For the other five tasks >50% of participants completed each task error free and those who did make errors made a median of 1–2.5 errors per task depending on the task. The maximum number of errors made by a single participant on a single task was 3 and the maximum number of errors made by a single participant across all tasks was 4. The task which had the most errors made was selecting the generate button (median: 2.5; IQR: 0.5; among participants who made errors). Mean time to task completion was positively correlated with mean number of errors made ($r = 0.6796$, $p = 0.0053$).

Interpretation of Map Visualizations

Users evaluating the map visualizations were asked three questions which involved interpreting the generated maps. Eight of the nine participants correctly answered all three questions which required interpretation of the visualization. One participant was only able to correctly answer one of the three interpretation questions.

Interpretation of 2-Dimensional Temporospatial Diagrams

Users evaluating the 2-dimensional temporospatial diagrams were asked four questions which involved interpreting the generated diagram. Only three of the eight participants correctly answered all four questions which required interpretation of the diagram. Three participants were able to answer three of the four questions correctly, and two participants were able to answer two of the four questions correctly. The most incorrect answers were given on the first question asked (4/8 participants answering incorrectly), as the questions advanced less errors were made and all participants correctly answered the fourth interpretation question.

Qualitative Analysis of User Experience

Using inductive thematic analysis three common themes (with 11 subthemes) were identified: comments on the user interface, comments on the visualization tool(s), and suggestions for improvement (**Table 2**). The number of times each subtheme was mentioned and the number of participants who mentioned each subtheme is shown in **Table 2**. All but three subthemes appeared in both the geographic map and 2-dimensional temporospatial diagram users.

Among comments on the software's user interface, the complexity of data entry was mentioned most frequently (five times by four geographic map users and nine times by five 2-dimensional temporospatial diagram users) (data entry panel is shown in **Figure 1**). This complexity was mentioned in positive and negative comments, sometimes by the same user. The majority of the comments were negative referencing both the length of time data entry would take "*I just wonder if there's a better way if you have to fill out the whole form. It's a bit of tough read and try and do quickly,*" that "*some of the fields are very similar and that was confusing,*" and "*the user may not know all these things.*" However, other participants mentioned that having a large number of variables to enter or adjust was a positive aspect. Approximately half of the participants in each group commented that the software was easy to use and five of the eight 2-dimensional temporospatial diagram users commented that they liked being able to compare the visualizations side by side. None of the map users made this comment although this feature was also available to them.

Several comments were made on the visualization tools themselves. Six of the nine map users mentioned that the opaque color coding hindered their ability to find exact locations on the map and would prefer either a semi-transparent color coding system to allow geographic features to be seen underneath or for road infrastructure and city/town names to be on the top layer of the map. **Figure 3** displays a side by side comparison of the same map with color coding set to 100% opacity (top panel) and 50% opacity (bottom panel).

> *"The primary thing I would like to see if I was using the software is that the opacity is at 50% always or if you had another layer where the roads cities and towns were in front always."*

There was disagreement among the users if the visualizations were simple and clear or if they were too complex (**Table 2**). Six of nine map users and two of eight 2-dimensional temporospatial diagram users mentioned the visualizations being informative and eight of nine map users and six of eight 2-dimensional temporospatial diagram users mentioned they or their colleagues would use this tool in their work. As illustrated in the two quotes below the use of this tool was viewed differently by those in different aspects of acute stroke care.

> *"I think there is an application for EMS [emergency medical services] for sure. Part of our destination protocols is where I see this working. It's significantly better than what we use now for sure. We are making a best-case judgement on where to take people but there is a lot of factors that affect the treatment people get especially in a rural centre but if you had a way to know the numbers … this could really lead you to the right place for sure."—Paramedic*

> *"…with this condition [stroke] it's very specific and it think this would help with infrastructure planning and planning in general. The potential to use tools like this for other conditions as well would be fascinating. Absolutely, I would use it. It takes a lot of complex information and it helps us visualize some of the terms*

TABLE 2 | Common themes from inductive thematic analysis.

Common themes with subthemes	Geographic map visualizations (*N* = 9)		2-dimensional temporospatial diagrams (*N* = 8)	
	Number of times theme mentioned	Number of users who mentioned theme	Number of times theme mentioned	Number of users who mentioned theme
1. Comments on user interface				
1.1. Complexity of data entry				
1.1.1 Positive	2	2	2	2
1.1.2 Negative	3	2	7	4
1.2. Ease of use	5	4	9	4
1.3. Liked compare view feature	0	0	5	5
2. Comments on visualization tool(s)				
2.1 Map opacity negatively effecting readability	9	6	N/A	N/A
2.2. Visualization simplicity				
2.2.1. Simple	1	1	3	2
2.2.2. Too complex	3	1	5	3
2.3 Mentioned visualization being informative	13	6	2	2
2.4 Would use this tool in their work	8	8	7	6
3. Suggestions for Improvement				
3.1 Auto population of data or having real time data updates	11	7	12	4
3.2 Addition of helicopter or fixed wing air ambulance	6	4	2	1
3.3 Suggested making map area searchable	9	4	N/A	N/A
3.4 Improve map loading speed	15	6	1	1

for future planning... To have something like this ... you can weigh your options, current performance, improved performance, and then even with improved performance, is there still a gap or a need in the area for more infrastructure?"—Health Care Administrator

The final theme that emerged was suggestions for improvement of the software and/or visualizations. The most common suggestion made was to auto populate certain data fields and/or have data updating in real time (mentioned a total of 23 times by 11 users). *"Having that ability for real time pre-populated info—as you know time is everything for this [stroke]."* Many users also mentioned improvements to map loading speeds would be beneficial. A common suggested addition to the visualization was the option to view helicopter or fixed wing air ambulance as a transport option for the patient (mentioned eight times by five participants). Lastly, four participants mentioned that making the map area searchable would improve the user experience.

DISCUSSION

This study displayed the usability of a novel visualization software for acute stroke pre-hospital transportation decision making. Both the geographic visualization and the 2-D temporospatial diagrams were relatively easy to use, as all participants were able to complete all tasks with minimal errors in a relatively short amount of time, with no prior training. There was significant variability in time to complete the study tasks among the participants (range: 53 to 184 s in the geographic visualization group and 42–106 s in the 2-D temporospatial diagram group). Time to complete tasks was significantly correlated with errors made in both study groups and as such we expect if users either received training on software operation or were allowed more time to self-learn the software the number of errors and therefore time to complete tasks would decrease. However, the group of participants had high self-rated computer proficiency which could influence these results; it is unknown if the software ease of use would be the same for users with lower computer proficiency.

In terms of interpretability the map visualizations may be more easily interpretable than the 2-D temporospatial diagrams (89 vs. 37.5% of participants correctly answering all interpretation questions). However, the intent of this study was not to compare the two visualization methods so further research would be needed to evaluate this. It was found that during the study as the questions advanced participants were able to make correct interpretations more often, thus with training and increased software familiarity we expect the interpretability of the visualizations to increase.

The majority of study participants felt that the software would be helpful for their work. As mentioned specifically by some participants in health care administration and paramedic roles this software could be used to develop acute stroke transport protocols through a more evidence-based tool that models this complex problem into a simple visualization. This is

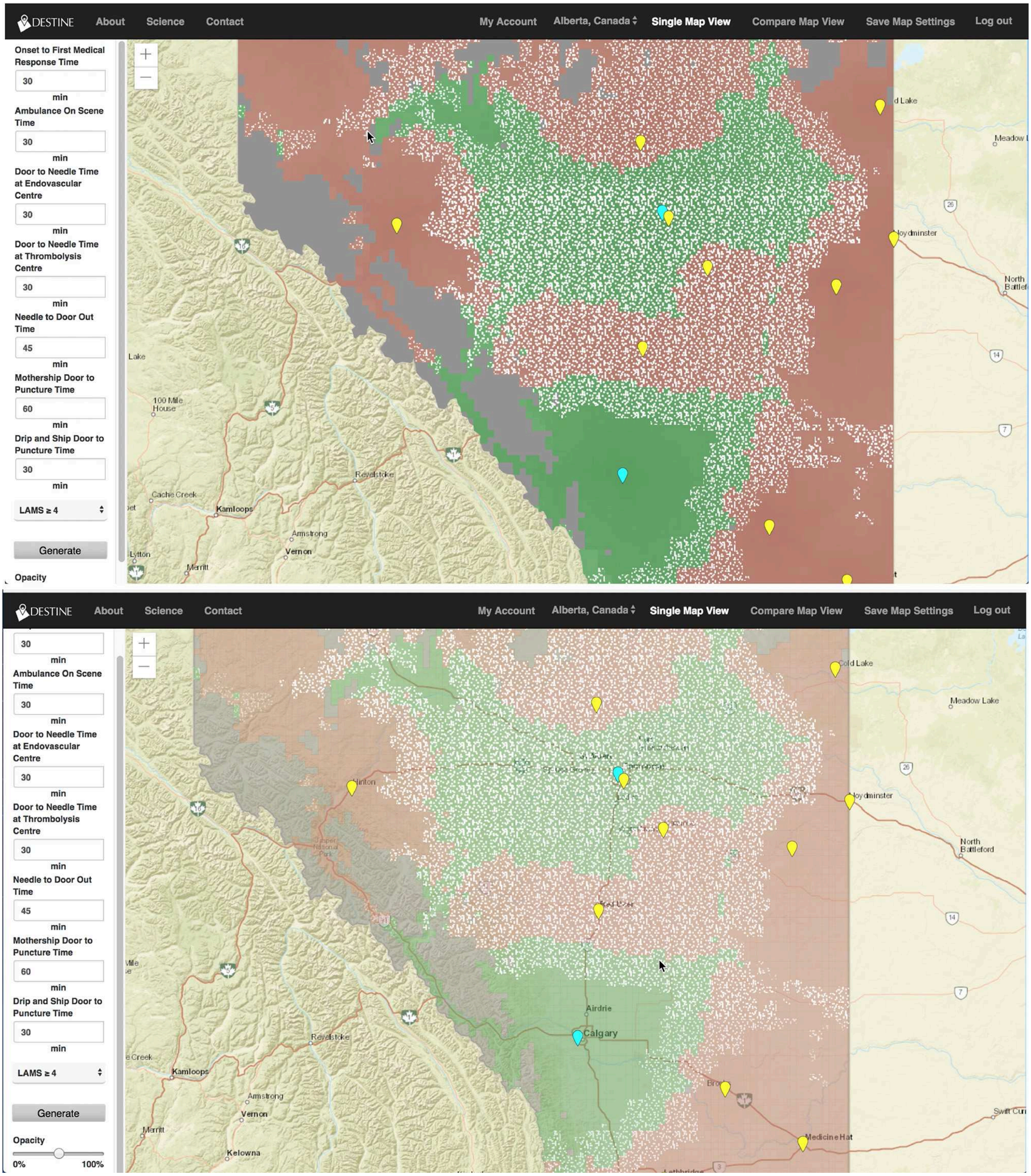

FIGURE 3 | Generated map from the DESTINE software (v0.01) showing Alberta, which was used in the usability tests. The top panel shows the map generated with 100% color coding opacity and the bottom panel shows the map generated with 50% color coding opacity so that the underlying major road structures and city names can be seen. The slider bar which changes the color coding opacity is shown in the bottom left corner of the bottom panel.

consistent with a case study that was previously performed with healthcare administrators using similar geographic visualizations using this model (but not using the software itself) (21). In the future additional studies could be performed on the impact of integration of a software such as this into decision making processes.

This study has allowed us to understand features which could be added to or changed in the software to improve the user experience. Based on feedback from the participants, two of these features are the addition of a search feature to search specific map locations as well as a more user-friendly way to change the transparency of the color visualization so that the map below it is more visible. Other items identified by the participants including the addition of air transport options and data pre-population will be the subject of future research.

There are some limitations with this study. Primarily, most 2-D temporospatial diagram participants when given free-time to use the software, found the mapping feature of the software on their own and explored it, as such some of their comments may be influenced by their use of the map view. Conversely, the opposite scenario never happened, no map participants explored the 2D temporospatial diagrams on their own. The study was performed on a relatively small number of individuals. Repeating the study in a larger sample may reduce variability in some of the quantitative measures, however in the qualitative analyses idea saturation was very quickly reached so it is unlikely that more participants would significantly impact these results. Additionally, the study could be repeated with participants in a different geographic setting to further validate the results. Finally, these results show the first use of the DESTINE software by a variety of healthcare professionals. It is anticipated that there will be a learning effect as users spend more time with the software. A follow-up study with long-time users of DESTINE would reveal additional information about the software's usability and additional features required.

Based on the results of this study healthcare professional from several different aspects of stroke care see geographic visualizations in stroke transport decision making to be a useful tool. The proposed usages varied based on healthcare professional type. The software demonstrated high usability as all participants were able to complete all tasks in a reasonable amount of time. However, several suggestions were made to improve user experience as well as additional features which could be developed and become the subject of future studies.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study reviewed and approved by the Conjoint Health Research Ethics Board at the University of Calgary with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

DISCLOSURE

JH and NK hold the copyright for the DESTINE software. Information on software use and licensing can be obtained on www.destinehealth.com.

AUTHOR CONTRIBUTIONS

JH and NK conceived and designed the study, performed and interpreted analyses, and wrote the manuscript. MF conducted the usability sessions and assisted in data analysis. MG and MH edited the manuscript for important intellectual and clinical content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00694/full#supplementary-material

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REVIEW
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Improving Prehospital Stroke Services in Rural and Underserved Settings With Mobile Stroke Units

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In acute stroke management, time is brain, as narrow therapeutic windows for both intravenous thrombolysis and mechanical thrombectomy depend on expedient and specialized treatment. In rural settings, patients are often far from specialized treatment centers. Concurrently, financial constraints, cutting of services and understaffing of specialists for many rural hospitals have resulted in many patients being underserved. Mobile Stroke Units (MSU) provide a valuable prehospital resource to rural and remote settings where patients may not have easy access to in-hospital stroke care. In addition to standard ambulance equipment, the MSU is equipped with the necessary tools for diagnosis and treatment of acute stroke or similar emergencies at the emergency site. The MSU strategy has proven to be effective at facilitating time-saving stroke triage decisions. The additional on-board imaging helps to determine whether a patient should be taken to a primary stroke center (PSC) for standard treatment or to a comprehensive stroke center (CSC) for advanced stroke treatment (such as intra-arterial therapy) instead. Diagnosis at the emergency site may prevent additional in-hospital delays in workup, handover and secondary (inter-hospital) transport. MSUs may be adapted to local needs—especially in rural and remote settings—with adjustments in staffing, ambulance configuration, and transport models. Further, with advanced imaging and further diagnostic capabilities, MSUs provide a valuable platform for telemedicine (teleradiology and telestroke) in these underserved areas. As MSU programmes continue to be implemented across the world, optimal and adaptable configurations could be explored.

Keywords: mobile stroke unit, rural health, prehospital, telemedecine, telestroke

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INTRODUCTION

Stroke is one of the most frequent causes of disability and death worldwide (1, 2). Acute ischaemic stroke has enormous societal and financial costs due to rehabilitation, long-term care, and lost productivity (3). Due to rapid advances over the last decades, there are now safe and effective treatments for stroke (4, 5). However, leading therapeutic modalities, intravenous thrombolysis, and mechanical thrombectomy are extremely time-dependent (6–9). International guidelines now support the use of thrombolysis up to 4.5 h after symptom onset as well as mechanical thrombectomy as a viable option within 6–24 h of last known normal for select patients with a mismatch between clinical deficit and infarct (4, 5). However, urgency remains as in case of mechanical thrombectomy, as for each 30 min delay before reperfusion, the relative likelihood of a good clinical outcome decreases by approximately 15% (10, 11).

With this in mind, concerted efforts have been made to improve in-hospital management of stroke by minimizing delays and optimizing protocols and personnel. However, despite substantial efforts to streamline care, a limited number of patients receive thrombolysis and fewer than 1–2% receive mechanical thrombectomy (12, 13). According to a recent survey of European stroke experts, 7.3% of ischaemic stroke patients in Europe received thrombolysis with 13 countries reporting rates higher than 10% with the highest rates in the Netherlands (20.6%), Denmark (19.%) and Austria (18.4%), and lowest of <1% (14). Thrombolysis rates vary both between and within nations, with rates as high as 28.5% in the German state of Baden-Württemberg compared to the national-level rate of 17.5% in Germany (14, 15). Furthermore, thrombolysis rates have continued to increase over time—for example, increasing from 4.0% (2003–2005) to 7.0% (2010–2011) in the United States—and continue to increase after publication of large trials (such as ECASS III) which have expanded 3- to 4.5-h since onset window (13, 16). These low rates of treatment are largely due to the fact that patients do not reach the hospital in time for assessment and treatment within the narrow therapeutic windows. In fact, only 15–60% of acute stroke patients arrive at the hospital within 3 h after onset of symptoms (17, 18).

The Mobile Stroke Unit (MSU)—first proposed and studied in Homburg, Germany—is an innovation in the prehospital phase which aims to address this urgency by bringing the hospital to the patient (**Figure 1**) (19, 20). This is achieved by equipping an ambulance with the necessary tools for diagnosis and treatment of acute stroke or similar, time-sensitive emergencies. Thus, in addition to standard ambulance equipment, the MSU is equipped with a small-bore portable CT scanner, a point-of-care laboratory, and stroke medication. Via incorporated telemedicine, CT images, and real-time videos can be bidirectionally transmitted between the hospital and ambulance for expert consultation. These images can be integrated with hospital medical records. With the point-of-care laboratory, hematological parameters (thrombocytes, erythrocytes, leukocytes, hemoglobin), coagulation parameters [international normalized ratio (INR), activated partial thromboplastin time (aPTT)], clinical chemistry parameters (gamma-glutamyltransferase, pancreatic amylase, creatinine, glucose), and others can be analyzed within minutes in the MSU (19–36).

With MSUs, earlier thrombolytic therapy—within the first, or golden, hour—after acute ischaemic stroke has been shown to be beneficial for patients with improved functional outcomes—for both patients who were independent and those who needed assistance in activities of daily living before their stroke (28, 37–40). When compared to hospital-based thrombolysis in the first hour after acute stroke, MSUs have been shown to have comparable functional outcomes and mortality at 3 months (41). MSUs have been shown to facilitate shorter alarm-to-treatment times without increasing adverse events (such as secondary intracerebral hemorrhage) (19, 28).

MSUs have been shown to play an integral role in evolving stroke services. They have been demonstrated to be effective in improving key prehospital temporal metrics (such as alarm-to-therapy and alarm-to-imaging times) in many centers worldwide (19, 25, 28, 29, 34, 42, 43). However, there remain relevant stroke treatment gaps for rural patients. MSU models and services can be adapted to improve stroke services for these patients. In addition to acute stroke triage, here, MSUs can provide telemedicine services to patients who are underserved. As stroke services continue to evolve, it is important to consider both the core and additional services which can be provided by MSUs.

INCORPORATING MSUs INTO STROKE SERVICE PLANNING

Primary Stroke Centers and Comprehensive Stroke Centers

The organization of acute stroke care has evolved significantly during the past few decades (**Figure 2**) (44). Primary Stroke Centers (PSCs) have been implemented to improve stroke care. PSCs include acute stroke teams, stroke units, written care protocols, and an integrated emergency response system (45). Comprehensive Stroke Centers (CSCs) integrate specialized services for the management of most severe cerebrovascular disease. These are typically staffed with experts in neurointervention and vascular neurology, have advanced round-the-clock, neuroimaging capabilities including MRI and cerebral angiography, specialize in surgical and endovascular techniques (including clipping and coiling of intracranial aneurysms, carotid endarterectomy, and intra-arterial thrombolytic therapy), and have specific infrastructure such as an intensive care unit (46).

As of 2017, comprehensive stroke centers accounted for roughly one-third of all stroke centers in the United States (327 of 1,148) and in France (37 of 132) (47–49). Considering large, densely populated European countries, the number of endovascular therapy capable centers range from 135 in Germany (1.7 per million inhabitants) to 28 in the United Kingdom (0.1 per million inhabitants) (14). In Finland, an example of a sparsely populated country, 5 of all 333 hospitals met criteria for classification as comprehensive stroke centers (50). In 2011, 66% of Americans were within a 60 min ground transfer to a primary stroke center (51). However, only 56% of Americans had 60 min ground transfer proximity to a CSC (52). As a result, in some settings it is difficult to transport patients directly to CSC, especially with standard ambulance services. Population distribution and density are important to consider when planning stroke services.

Onsite Triage to Avoid Secondary Transfer and In-Hospital Delays

Accurate triage and selection of the appropriate target hospital avoids the transfer of patients with large-vessel occlusion to hospitals without endovascular treatment services. It is estimated

FIGURE 1 | Mobile Stroke Unit (MSU). The Mobile Stroke Unit is an ambulance which contains a multimodal CT scanner, a point-of-care laboratory, as well as a telemedicine system, which allows transfer of CT images and videos of patient examination for input from hospital specialists. Pictured is the MSU in Homburg, Germany.

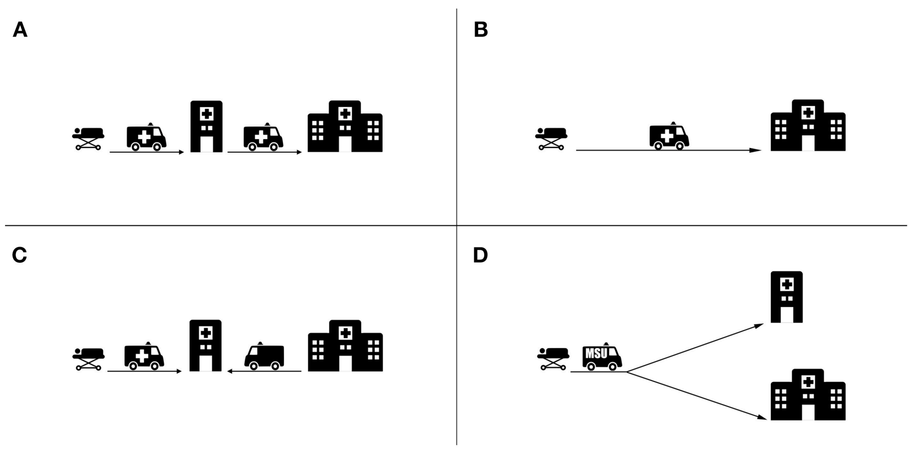

FIGURE 2 | Main transport strategies for acute stroke patients. **(A)** Drip and Ship strategy whereby the patient is transported from the emergency site to a PSC for thrombolysis and then further transported to a CSC for thrombectomy. **(B)** Mothership strategy whereby the patients is transported directly to the CSC, bypassing the PSC. **(C)** Specialist Rendezvous strategy (sometimes called "flying" doctor) whereby the patient arriving at the PSC is met by an interventionalist from a CSC. **(D)** MSU Strategy whereby triage decisions are made at the emergency site and the patient is transported based on the diagnosis to a PSC or CSC where appropriate.

that every minute of delay in transfer reduces the probability that patients will receive intra-arterial treatment by 2.5% (53). Further, by identifying thrombectomy-eligible patients, appropriate triage prevents the overloading of comprehensive stroke centers.

The MSU strategy has been shown to be effective for the triage of stroke patients (54). CT-angiography has been used in MSUs to assess for LVO at the emergency site (19). Even use of non-contrast CT has been associated with reduction of delay before intra-arterial treatment (30). For patients with haemorrhagic stroke, MSU-based triage allows for transport to hospitals with neurosurgery services, bypassing hospitals without such capabilities (26). In the urban setting of Berlin, patients with hemorrhage transported to hospitals without neurosurgery services decreased from 43% in the conventional treatment group to 11% in the MSU group (43, 55). MSUs are also valuable for investigating other time-sensitive cerebral conditions such as traumatic brain injury or status epilepticus (56).

STROKE TREATMENT GAPS FOR RURAL PATIENTS

For rural patients, distance and travel time to the nearest stroke center is a crucial issue for time-sensitive stroke treatment (57, 58). Times from symptom onset to rural hospital admission range from 5 to 30 h have been reported (59, 60). These transport delays contribute to the low rate of thrombolysis of 1–6% for patients in rural areas worldwide (61, 62). Further, rural-urban disparities in thrombolysis administration have increased in recent decades (63). This trend is seen not only in low and middle-income countries but also in high-income countries (59, 64, 65). In Australia, only 3% of rural patients were able to access stroke units in a timely manner compared to 77% of urban patients (66). In Canada, patients living in rural areas are less likely to receive stroke unit care, brain imaging within 24 h, carotid imaging, and neurologist consultations. Furthermore, rural patients were less likely to be transferred to inpatient rehabilitation facilities and less likely to receive physiotherapist, occupational therapist, and speech and language therapist review (67). In the United States, the Get With the Guidelines—Stroke Registry has identified the arrival to a rural hospital as one of the factors associated failure of thrombolytic therapy (68).

The treatment gap between urban and rural areas is even more pronounced with endovascular treatment options for acute stroke (69). For the provision of intra-arterial therapy, the center requires highly specialized staff (such as vascular neurologists, neurointensivists, neuroradiologists, and anaesthesiologists), capable facilities and technical resources. This complex infrastructure is only available in limited CSCs which are located almost exclusively in urban centers (70). Consequently, patients living in rural and remote areas have limited access to timely IAT services (71).

Several strategies have been implemented in an effort to increasing thrombolysis rates. Health system factors generally associated with higher thrombolysis rates are urban location, centralized or hub and spoke models, treatment by a neurologist/stroke nurse, in a neurology department/stroke unit or teaching hospital, being admitted by ambulance or mobile team and stroke-specific protocols (72). Thrombolysis rates may be dependent on the hospital's level of stroke service (with stroke centers having the highest rates and hospitals without stroke units having the lowest rates) and patient factors such as age and preexisting disabilities (15). Accordingly, organizational streamlining by bypassing hospitals without stroke units may be sensible. However, in sparsely populated areas with long distances to the nearest stroke unit, it may be reasonable to initiate thrombolysis at a local hospital (supported by telemedicine, if available) before transferring the patient to center with a higher level of stroke care (73).

ADAPTING MSU APPROACHES TO RURAL HEALTHCARE

MSUs provide a valuable resource to rural and remote settings where patient may not have easy access to in-hospital stroke care (74). The MSU model can be adapted to local settings based on local needs. Accessing telemedicine technologies through cellular communication provides instant information enabling healthcare providers to reach out beyond the doors of the hospital.

As MSUs typically look to integrate with local emergency response services, there are several models of MSU staff composition. On board personnel can include vascular neurologists, paramedics, nurses or radiographers (25). Staff composition can be adapted to address the need of rural settings. In Norway, MSU staffing and responsibilities have been developed to work together with the existing EMS framework for rural and remote health (32, 75–77). In these smaller urban areas, the MSU is staffed with an anaesthesiologist, a paramedic and a nurse paramedic. Anaesthesiologists have been trained to identify and treat stroke (76). The anaesthesiologist may also provide resuscitation and perform invasive emergency procedures to any unstable or critically ill patient (77). Evolving telestroke technology requires staff to have ongoing, intermittent or mock training (78).

Subsequent iterations of the MSU have adapted to their respective settings. Larger vehicles have the advantage of carrying larger scanners and more specialized personnel, robustness in rural off-road conditions, and allowing relatives to accompany patients to provide history and procedural consent (79). Smaller vehicles may have greater access to narrow roads and lower cost. With this in mind, vehicle models should be selected according to the specific needs of the region and healthcare setting (25).

In Australia, a potential solution to serving remote patients with an Air Mobile Stroke Unit (Air-MSU) is being explored (80). With this approach, the MSU concept is being extended to another transport vehicle by equipping a helicopter or airplane with the CT scanner, POCT, and telemedicine connectivity.

A rendezvous model has been studied to enable the MSU cover large rural areas (**Figure 3**). With this approach, a conventional EMS ambulance is dispatched to the patient location and then travels toward the hospital. The EMS ambulance is met at

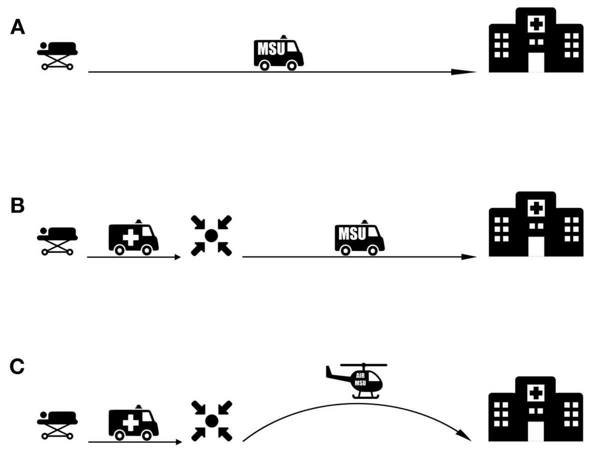

FIGURE 3 | MSU-based transport strategies for patients with LVO. **(A)** An MSU-based model where imaging and triage is performed onsite and the patient is transported directly to a CSC. **(B)** Rendezvous approach extending MSU range for rural areas. A conventional ambulance transports the patient to a rendezvous point with the MSU. After MSU-based imaging and diagnosis, the patient is transported directly to a CSC. **(C)** Proposed Rendezvous approach with an Air-MSU suitable for remote areas with large transit distances.

predetermined rendezvous locations—approximately half the distance—by the MSU. Predetermined rendezvous points are selected based on factors including catchment area, ease of road access, road connectivity and wireless signal strength (35). In a large rural area in Northern Alberta, Canada, this rendezvous approach has increased the catchment area to a 250 km radius surrounding the Comprehensive Stroke Center (35). This approach can be adapted to urban areas close to the periphery of the MSUs direct response area, effectively increasing the catchment areas of these units.

For rural and remote patients, there are also opportunities for incorporation of the MSU concept with the air ambulance service. In these situations, the air ambulance can act as the first responding vehicle to meet and transport the patient. Here, the patient can be transported to a predetermined rendezvous point or to a PSC where the patient can be met by the MSU. For a proposed Air-MSU, the CT-equipped airplane may land at the emergency site, and undertake onsite specialized stroke care and imaging (80). Alternatively, conventional EMS (ground or air) can meet the patient at the emergency site and transport the patient to a rendezvous point or PSC where the patient is met by the Air-MSU.

COST EFFECTIVENESS

While the MSU strategy remains an innovative approach to prehospital acute stroke management, more data is required to best understand the costs of the MSU, its staffing, and operation. Two independent preliminary analyses of cost-effectiveness have reported encouraging results. Based on the Homburg trial, analysis demonstrated an improvement in cost-benefit with reduction of personnel and an optimal cost-benefit with an operating radius between 43.01 and 64.88 km (81). In an analysis of Berlin-based MSUs, a higher rate of thrombolysis and earlier treatment for MSU patients resulted in reduced disability and its associated costs (82). While both of these studies suggest cost benefits, prospective cost efficiency data comparing MSUs to standard management is expected and awaited from the BEST-MSU trial (83).

MSU cost-effectiveness may be improved by substituting onboard physicians for telemedicine-linked remote experts (84). Considering the onboard CT scanners, there is the possibility for increased demand and improved technology to help reduce this high startup cost as economies of scale take their effect (85). Future services may be expanded to include other cerebral emergencies and treatment modalities.

Considering rural and underserved areas, the cost impact of frequency of deployment, operational area, personnel costs and support or replacement of other services may differ from urban settings and trial scenarios. MSU programmes may involve single or multiple units to cover large geographic areas and may require additional co-ordination with local EMS if, for example, a rendezvous approach is taken. Payment and reimbursement models particular to a health care system would impact cost burden to emergency and hospital services (86). In some rural settings, ambulance agencies may not be directly affiliated with the relevant hospital impacting costs for the health services involved (74).

Future prospective research is required in defining costs for establishing and maintaining MSUs and costs for both acute and long-term care of patients managed both on MSUs and by standard emergency services. It is important that this financial cost is weighed with the perspective of important stakeholders in acute stroke care and consideration of total hospital and long-term care costs to the health care system for each stroke patient. As MSU configuration and operation is influenced strongly by setting, further health economic analyses in a variety of settings are required.

TELEMEDICINE FOR MSUs

Telecommunication approaches between MSUs and the stroke center via systems can provide real-time remote specialist advice by teleradiology (transmission of high-quality images) and telestroke assessment (real-time bidirectional videoconferencing and high-speed videos transmission) (25). As such, MSUs can provide advanced imaging and expert consultation at either the emergency site or at smaller healthcare centers which otherwise would not have this capability.

Teleradiology enables the transmission of images and information to physicians and specialists for use in remote diagnoses and medical consultation. Through MSU-based teleradiology high-resolution medical images (such as CT scans) can be obtained onsite, transmitted while stationary or en route, and interpreted by experts at a major university medical center.

Telestroke planning can be organized into a distributed network or hub-and-spoke model. In a distributed network model, the telestroke specialist is affiliated with a third party employer which provides contracted services with the originating hospital site (87). In a hub-and-spoke model, specialty care is provided to patients at community settings (spokes) by specialists affiliated with larger, more comprehensive tertiary care centers (hubs). Spokes are primary and secondary care centers which can be linked to distant sites—even more than 300 km away—where the telestroke provider is located. At hubs, vascular neurologists and other acute stroke specialists compose a call panel delivering telestroke services (78). Hubs further act as recipients for patients which require transfer to a higher level of care. Hub-and-spoke models have been shown to be cost-effective and to increase the catchment population (88, 89).

Reliability of MSU-Based Telemedicine

Technical innovation in the transmission of data between the hospital and MSU plays an important role. Early studies encountered difficulties in telecommunication in part due to suboptimal 3G public network availability (90–94). Fortunately, with improved technology and 4G mobile systems telecommunication is becoming more reliable (25). Telemedicine encounters between the MSU and hospital have been shown to be successfully completed for 99% of patients with 4G connectivity (95). Low-cost, tablet-based platform via commercial cellular networks (4G/LTE) were used to reliably perform prehospital neurologic assessments (NIHSS) of actors in both rural (central Virginia) and urban settings (San Francisco Bay Area) via videoconferencing (96). With innovation it is important to ensure that bidirectional telecommunication is encrypted, secure and meets standards for transmission of protected health information.

The reliability of MSU-based telestroke assessment has been evaluated. Remote stroke assessment through telemedicine by a vascular neurologist has been shown to be reliable and comparable to in-person assessment (94). Further treatment decisions for thrombolysis showed strong agreement between an on-board vascular neurologist and a telemedicine vascular neurologist (84). The level of agreement is comparable to two vascular neurologists evaluating the same patients face-to-face in the emergency department (97). Importantly, the time to treatment decision and thrombolysis administration has been shown to be comparable between on-board and telemedicine vascular neurologists (98).

Limitations

While MSU-based telestroke approaches are promising, there are limitations to the management tasks which can be carried out remotely. The treatment of acute stroke in an MSU is a complex exercise involving multiple parallel tasks being carried out by several healthcare professionals within the confined space of an MSU. This includes neurological assessment, monitoring of vital signs, patient positioning, management of patient comfort, and possible restraint, CT scanning, point-of-care laboratory testing, and medication preparation and administration (86). Furthermore, the clinical decision on whether to administer thrombolysis requires training, experience, and careful clinical judgment. As such, there may be a limit to clinical decisions which can be carried out in the physical absence of a vascular neurologist via telemedicine. Looking beyond the first hour's hyperacute care, stroke patients require ongoing care from physiotherapists, occupational therapists and speech and language therapists. When considering the extension of stroke care to rural and underserved areas with MSUs, further work is required to determine optimal models for integration of these services.

EMS response varies worldwide, including between many European and US MSU settings. In the United States, ambulances are typically not staffed by physicians. As a result, in developing an MSU programme, a decision has to be made as to whether to include an on board physician. Early experience from Houston suggests the ratio of MSU alerts from EMS dispatch to tPA treatments is up to 10 to 1, suggesting that it may be impractical to have a vascular neurologist aboard the MSU for all calls (86).

IMPROVING PREHOSPITAL STROKE CARE IN LOW AND MIDDLE-INCOME COUNTRIES

With rapid advances in prehospital stroke care primarily in high-income countries (HIC), it is important to consider opportunities, challenges and the applicability of these approaches to low and-middle income countries (LMIC) as well. There is a growing disparity in the burden of stroke between LMIC and HIC. About 75% of deaths from stroke and more than 80% of disability-adjusted life years (DALYs) occur in LMICs (99–103). Further, in the last four decades, there has been a 42% decrease in stroke incidence in high-income countries and a 100% increase in LMIC (104). Cerebrovascular diseases in sub-Saharan Africa are increasingly frequent and associated with a poor outcome (2, 105–111). Unfortunately, there is very limited data on the organization of prehospital stroke services in such settings. For example, only 3 African countries (South Africa, Egypt, and Morocco) have reported experiences on thrombolysis (112).

There are multifactorial barriers to implementing effective prehospital stroke care in the LMIC setting. Prehospital barriers include unavailable/inadequate transportation and a lack of trained stroke specialists (101, 102, 113). Considering transport, in many cases, the ambulances are not well-equipped and do not have trained personnel (114). Further, most patients in these settings use their personal or hired vehicles, rather than ambulances, to seek medical help (113, 115). In these settings, patients who are transported by ambulances are predominantly those with trauma injuries and obstetric emergencies (113).

The global deficit in skilled healthcare personnel is most pronounced in rural areas, especially in LMIC (114, 116). In India, 80% of specialists live in urban areas. Consequently, 700 million people living in rural India have to travel a distance of 75 to 100 km for a tertiary consultation (117). There remains a paucity of neurologists worldwide, especially in the LMIC setting. The global median of adult neurologists is 0.43 per 100 000 population, with the number of adult neurologists ranging from 0.04 (in LIC) to 4.75 (in HIC) per 100,000 population (118). In India, nearly 1 billion people live in regions lacking access to a practicing neurologist (119).

With limited specialized personnel and transport available, telemedicine could be helpful to address gaps in stroke service delivery. Remote teleconsultations would allow the few, existing specialists, primarily situated in urban areas, to provide expertise to a greater number of patients who are situated in rural settings. To overcome infrastructure and connectivity hurdles, satellite-based telemedicine has been effectively employed in rural India (120).

A telemedicine-capable MSU could provide specialized care in the regions with limited hospital emergency departments and lacking EMS systems. MSUs could function as mobile clinics when not in use in emergencies. As such, they could provide hospital-caliber imaging and laboratory services to underserved areas.

Encouragingly there are a growing number of MSU programmes in LMIC settings. For example, in Thailand, a stroke fast track programme, telestroke, and two MSUs in Bangkok are improving stroke care (121). Inclusion of MSUs should be considered as part of long-term planning for stroke service improvement in these settings.

MSU operation is influenced strongly by setting—be it urban or rural, or high- or low-income. In metropolitan settings, factors such as traffic congestion and existing emergency response configurations as well as geo- and socio-spatial determinants of emergency service utilization impact transport modeling (122). In LMIC, road conditions impact both transport planning and may necessitate physical upgrades to the MSU vehicle. However, data in these settings remains limited. As the preponderance of MSU studies to date have been conducted in HIC, further research is required better understand the implementation and optimization of MSU transport models in the LMIC setting.

Considering the prehospital phase as a whole, there are alternative strategies for early identification and preclinical selection of stroke patients which may have applicability to rural patients and those in resource-limited settings. Several prehospital stroke screening scales have been developed and employed in an effort to assist dispatchers in identifying stroke patients with high specificity and sensitivity (123–125). Additionally, there are several prehospital scales assessing stroke severity with the potential to help identify patients with LVOs (126–128). Nevertheless, prehospital stroke scales vary in their accuracy and may be influenced by levels of stroke scale training and provider educational standards (124, 129). Public awareness campaigns, training of dispatchers, and paramedics are also effective methods of early identification of stroke which may be complementary to other prehospital strategies (130–135). The quality of stroke care varies across the world depending upon location, local hospital facilities, ability to pay, education, and cultural, social, or religious beliefs (136). As such, prehospital strategies should be tailored to local health needs, affordability and existing stroke services.

FUTURE DIRECTIONS

Future MSU service planning may involve integration of multiple concepts. Further adaption will allow MSUs to better integrate into local and regional emergency medical services. Remote locations may eventually benefit from a combination of the Air MSU and rendezvous model. Specialized training of on board personnel may further alleviate the need for an on board vascular neurologist. Improvements in technology may allow for smaller, lighter and more robust units CT scanners. The MSU concept can be expanded to treat other emergencies in underserved areas. Further studies are required to better understand the medical and health-economic benefit of each model.

AUTHOR CONTRIBUTIONS

SM and KF contributed to the conception and design of the work, literature search, analysis and interpretation, and article drafting. SM, SW, IQG, SAH, ML, and KF contributed to critical revision. All authors gave final approval of the version to be published.

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Googling Boundaries for Operating Mobile Stroke Unit for Stroke Codes

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Background: Mobile stroke units (MSU) have been proposed to expedite delivery of recombinant tissue plasminogen activator (tPA) and expedite endovascular clot retrieval (ECR). Unexplored questions in the use of MSU include: maximal distance from base, time limit with regards to the use CT imaging, CT Angiography, CT Perfusion, and Telemedicine. We developed a computational model as an app (https://gntem3.shinyapps.io/ambmc/), taking into account traveling time to explore this issue. The aim of this study was to define the operating parameters for an MSU in a large metropolitan city, based on the geography of Melbourne.

Methods: There are 2 hospitals (Royal Melbourne Hospital/RMH, Monash Medical Center/MMC) designated to provide state-wide ECR services. In these spatial simulations, the MSU is based at RMH and delivers tPA at the patient's pick-up address and then takes the patient to the nearest ECR center. We extracted the geocode of suburbs in Melbourne and travel time to each hospital using *ggmap*, an interface to Google Map API. The app contains widgets for varying the processing time at the patient location (default = 30 min), performing CT angiography (default = 10 min), performing telemedicine consultation (default = 15 min). The data were compared against those for usual ambulance metrics (default traveling time = 15 min, processing time at patient's location = 20 min, door to tPA = 60 min, door to groin = 90 min). Varying the widgets allow the viewer to explore the trade-off between the variable of interest and time to therapy at a suburb level.

Results: The MSU was superior for delivering tPA to all Melbourne suburbs (up to 76 min from RMH). If the CTA times or processing time at location increased by 20 min then it was superior for providing ECR to only 74.9% of suburbs if the return base was RMH. Addition of CT Perfusion or telemedicine consultation affect the ability of a single hospital to provide ECR but not tPA if these additions can be limited to 20 min. Conclusion: The app can help to define how best to deploy the MSU across Melbourne. This app can be modified and used to optimize operating characteristics of MSU in other centers around the world.

Keywords: stroke, transport, modeling, optimization, Google Map

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INTRODUCTION

Stroke is a leading cause of disability worldwide and results in significant economic and societal cost (1). In spite of this, there is now substantial optimism with acute stroke management since the publication of pivotal trials for thrombolysis (2) and endovascular clot retrieval (ECR) (3–8). Substantial efforts go into providing thrombolytic therapy within the "golden hour." With this in mind several groups around the world have used mobile stroke unit or ambulance equipped with CT scanner to achieve this aim. The first randomized trial showed an absolute difference of 16 min from onset to treatment with TPA (9).

Several models of mobile stroke unit (MSU) are currently in existence. The Berlin model operates an MSU within 16 min radius from base (10). However, other models have not defined a clear distance from the treating hospital (11). It is not clear if the distance/time threshold described in the Berlin model also applies to Australia (or elsewhere). Further, the original MSU model was described in an ambulance performing only non-contrast CT (NCCT) (10) with the aim of providing faster tPA delivery. Since then, CT angiography (CTA) and Telemedicine have been added to MSU (2). However, it is not clear if CT Perfusion is currently in use on MSU (11). These latter additions permit exploration of triaging delivery of patients with large vessel occlusion to ECR-capable hospitals. Unexplored questions in the use of MSU include, maximal travel time from base, limit with regards to the time spent on use of additional CT imaging (CTA, CTP), and time spent using Telemedicine on board the MSU instead of having a stroke doctor on board. We propose the use of Google Map API for transport modeling of MSU in metropolitan cities in Australia (12).

The state of Victoria, Australia has set up a statewide service protocol and two hospitals designated as ECR hubs (Royal Melbourne Hospital/RMH and Monash Medical Center/MMC). The purchase cost of MSU has been estimated to be around US$ 750,000 to US$1,400,00 with annual running cost of around US$1,000,000 (13). As such, only one model is operating in Melbourne since 2017. By taking advantage of recent developments in the Google Map application program interface (API), we undertook this simulation study to develop and apply a computational method to objectively define the operating parameters for MSU in Melbourne from alarm to reperfusion therapy time.

METHODS

Setting

Melbourne is the capital city of the state of Victoria in Australia with a population of ∼4.9 million and population density of 12,400 per km^2 (http://www.abs.gov.au/websitedbs/). The postcodes for metropolitan Melbourne are in the range 3000–3207. These ECR hubs are required to provide a 24-h service not just for patients in their immediate local catchment but also for all residents of Victoria. These catchment of the ECR hubs is displayed at https://gntem2.github.io/Google-Map-to-Victorian-ECR-Hospitals/. In addition to these 2 centers, there are 2 further ECR capable hospitals and 6 non-ECR capable hospitals providing intravenous thrombolysis in metropolitan Melbourne.

Google Map API

We used *ggmap* to access Google Map application program interface (API) (https://developers.google.com/maps/). Ggmap is an open source software freely available written in R (R Project for Statistical Computing, version 3.4.4) (14). The Google Map "geocoding" API describes a location in terms of its geocode (latitude and longitude). We performed geocoding of the centroid of each postcode. The traveling time to and from each hospital in Melbourne was obtained from Google Map "distance matrix" API. We found the Google Map "distance matrix" API to be faster than the Google Map "direction" API; this is due to the latter also obtaining a direction matrix for each query.

Experiments

Currently, MSU operates within a 20 km radius from RMH. The spatial simulations were performed without restriction on operating distance. The MSU is assumed to be based at RMH and delivers TPA at the patient's location and returns to base (RMH) for ECR. In the second scenario, the MSU delivers patient to both RMH and MMC for ECR.

Optimization

We set up one set of linear equations for MSU and one for usual ambulance. The total sum of time taken for MSU and usual ambulance were compared to obtain the number of postcodes where one model is superior to the other in terms of time from alarm to reperfusion therapy time. The simulation for tPA was performed with default time to therapy for usual ambulance delivery (from pick up) set at 95 min and for ECR at 125 min. Due to the multiple ambulance hubs around Melbourne, we made the assumption for usual ambulance transport is that the patient is 15 min from the nearest ambulance, and that on arrival it takes 20 min to process the patient at the scene. These data were based on the validation data between observed ambulance time and Google Map API queries in our previous publication (12). In this study, it is assumed that each hospital can give tPA within 60 min of hospital arrival; this time include performing advanced imaging with CT Perfusion and CT Angiography (15). By contrast, MSU take a certain time to arrive at patient location, takes another 30 min to process patient at scene (including blood test). The CTA is assigned default time of 10 min to set up (inclusive of setting up contrast media injector and processing of images). It is assumed that once large vessel occlusion is identified the patient is taken to ECR hub for clot retrieval and that there is no need to the ECR hub to do further imaging. A processing time (default 30 min) at the hub is assigned for viewing CTA images and setting up ECR procedure.

The app contains widgets for varying the processing time at the patient location and performing non-contrast CT/NCCT (default = 30 min), performing CT angiography (default = 10 min), performing telemedicine consultation (default = 15 min) (16). The data were compared against those for usual ambulance metrics (default traveling time = 15 min, processing time at patient's location = 20 min, door to TPA= 60 min, door to groin = 90 min). Varying the widgets allow the viewer to explore the trade-off between the variable of interest and time to therapy at a post code level. The reader can choose to change these variables by going to the app. Internet connectivity is required for app access.

Web Based Display

The interactive web-based maps were generated using R package *leaflet* using tiles from OpenStreetMap (©OpenStreetMap contributors. For copyright see www.openstreetmap.org/copyright) (17). Next, these web pages were incorporated into app, written using Shiny, Rstudio, and is accessible at https://gntem3.shinyapps.io/ambmc/.

RESULTS

Using the default setting for tPA [MSU = 40 min (processing at scene = 30 min, CTA = 10 min)], MSU is superior to usual ambulance (95 min) in terms of time metric for delivering tPA to 100% of metropolitan Melbourne suburbs (see **Table 1**, **Figure 1**). Delivery of tPA in Melbourne can be done faster by tPA as far as 76 min from the base at RMH. Provision of ECR was superior to usual ambulance route in terms of time metric to 99.5% of suburbs if the patients are brought back to RMH for therapy. If MSU also uses MMC as a site for ECR then this model is superior in 99.5% of suburbs.

Improved Door to tTPA/Groin

If the delivery of therapy by usual ambulance route is faster by 10 min (by reducing door to tPA) then MSU is superior for ECR in 92.3% of suburbs when treatment is performed at base at RMH and 98.4% of suburbs when treatment can be performed at RMH and MMC (see **Table 1**). If the delivery of therapy by usual ambulance route is faster by 20 min, then MSU is superior for ECR by time metric in 74.9% of suburbs (treat at base) and 93.4% of suburbs (treat at base and MMC).

Addition of CT Perfusion to Imaging Protocol

Using time metric, MSU remained superior to usual ambulance for TPA in 99.5% of cases when CT Perfusion was added to the imaging protocol. Provision of ECR is superior to usual ambulance in 92.3% of suburbs if the patients are brought back to RMH for therapy. If MSU also uses MMC as site for therapy then this model is superior in 98.4% of suburbs (**Table 1**).

Addition of Telemedicine

The results for telemedicine was similar to that described above for CT Perfusion. Using time metric, MSU remained superior to usual ambulance for tPA in 99.5% of case when Telemedicine adds 10 min to the treatment time. When Telemedicine adds 20 min to the treatment time MSU remained superior to usual ambulance for TPA in 97.8% of suburbs and for ECR in 74.9% of suburbs when returning to base (RMH only) and 93.4% of suburbs when returning to either ECR hubs (RMH and MMC). When Telemedicine adds 30 min to the treatment time MSU remained superior to usual ambulance route for TPA in 93.4% of suburbs and for ECR in 39.3% of suburbs when returning to base (RMH only) and 63.9% of suburbs when returning to either ECR hubs (RMH and MMC).

Combined CT Perfusion and Telemedicine

Using time metric, MSU remained superior to usual ambulance for TPA in 96.2% of case when CT Perfusion was added to the imaging protocol. Provision of ECR is superior to usual ambulance in 58.5% of suburbs if the patients are brought back to RMH for therapy. If MSU also uses MMC as site for therapy then this model is superior in 83.1% of suburbs.

DISCUSSION

In this study, we described an objective method to explore operating characteristics of a MSU using time to therapy as metric of performance. Further, the time metric is displayed on a map of Melbourne, permitting optimization of the operating parameters at spatial level. The concept behind simulation to define operating characteristics of the MSU is that one cannot know prior to deployment the operating parameters of MSU. These parameters affect the choice of MSU e.g., addition of CT Angiography and CT Perfusion. Purchase of these additional equipment is expensive but may also negatively prolong the time to treatment. Further should the neurologist be on board or should it be staffed by trained nurse supported by telemedicine? The app can be used strategically for planning. Exploration of the app shows that MSU can be deployed across Melbourne (maximum range of 76 min for TPA). At this range and employing time metric for assessment, MSU is still superior for delivery of ECR if the 2 hubs model is used. The modeling approach described here can be used to define boundaries for operating MSU around the world.

The hypothetical range of MSU in our studies (76 min) is much further that used in Berlin (16 min, population 1.3 million) (10). It is not clear the reason for the short operating range in Berlin. However, operating MSU at long range may decrease capability to respond to another case especially in Melbourne which has a large catchment (∼4.9 million). Other models have not described the operating range but have described the population and which may serve as proxy for the catchment. The New Jersey model serves a modest population of 460,000 (13) and the Cleveland model serves a population of 390,000 (18). There are attempts to explore the use of MSU in rural setting in Germany (11). We use the app to propose the use of spatial simulation to help define the operating parameters of MSU.

The earlier studies described the use of MSU with NCCT capability only (10, 13, 16). As such the data regarding performance with CTA and CTP are not well known (11). Our study shows that the addition of further test such as CTP comes at the expense of reducing the operating distance for MSU. The idea behind using CTP to triage patients for tPA and ECR with go no go maps (salvageable tissue vs. large infarct core) (7, 19, 20). In this simulation, CTP did not confer a benefit as the metric of comparison with usual ambulance delivery was time based; further, this metric assumes that decisions are correctly

TABLE 1 | Effect of varying time MSU metrics on performance.

Usual ambulance to TPA/ECR (min)	MSU						
	Processing time (min)	CTA (min)	CTP (min)	Telemedicine (min)	Superior for TPA (%)	Superior for ECR (RMH) (%)	Superior for ECR (RMH and MMC) (%)
95/125	30	10			100	99.5	99.5
95/125	30	10	10		99.5	92.3	98.4
95/125	30	10		10	99.5	92.3	98.4
95/125	30	10	10	10	97.8	74.9	93.4
95/125	30	10		20	97.8	74.9	93.4
95/125	30	10		30	93.4	39.3	63.9
85/115	30	10			99.5	92.3	98.4
85/115	30	10		10	97.8	74.9	93.4
85/115	30	10		20	93.4	39.3	63.9
75/105	30	10			97.8	74.9	93.4
75/105	30	10		10	93.4	39.3	63.9
75/105	30	10		20	60.1	13.7	21.9

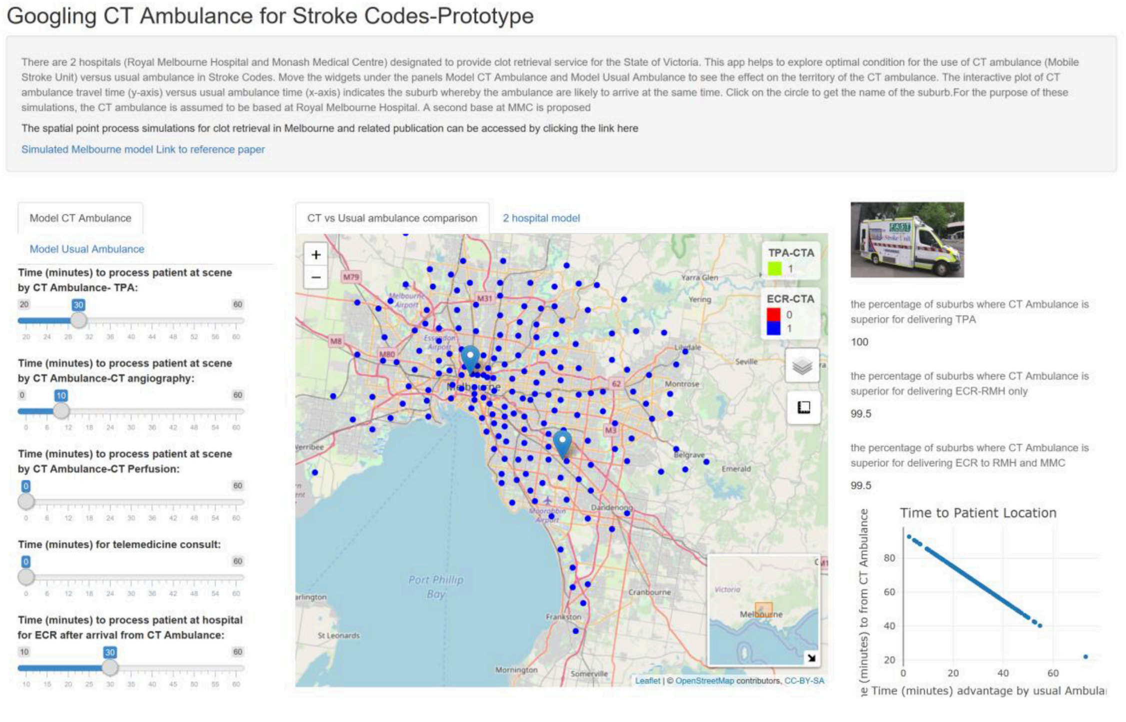

FIGURE 1 | The apps contain widgets (on the left side) for varying variables of interest for MSU and usual ambulance. The suburbs in which MSU is superior to usual ambulance is displayed on the map as green (inferior as yellow). The viewer can switch the control box to display suburbs in which MSU is superior for returning to base at RMH to perform ECR (blue). The percentage of suburbs in which MSU is superior to usual ambulance is displayed on the right-hand side. Using CTA & on-board neurologist, MSU can reach 100% of suburbs for TPA.

made with CTA. In this study, the default time for CTP was 10 min. This time included reloading the contrast media injector, acquire the scan and process the perfusion image. This time frame is what we have observed in a clinical scanner in our hospital. In the future, newer scanner may combine CTA and CTP into one image acquisition rather than 2 acquisitions at present. Additionally, the acquisition and processing time may reduce significantly. The viewer can explore this by moving the widget to a time below the default 10 min. In these future scenarios with improved scanner, it would be advantageous to perform CTA and CTP. The impact of these new technology on running MSU with Telemedicine will be expanded below.

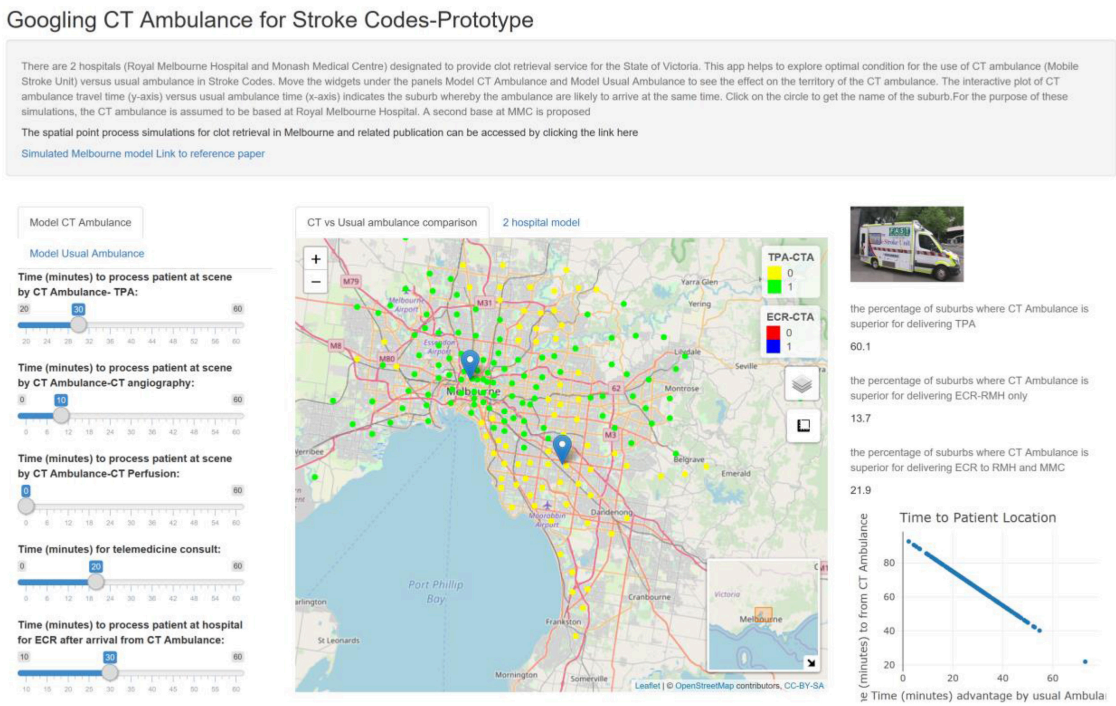

FIGURE 2 | The apps contain widgets (on the left side) for varying variables of interest for MSU and usual ambulance. The suburbs in which MSU is superior to usual ambulance is displayed on the map as green (inferior as yellow). The viewer can switch the control box to display suburbs in which MSU is superior for returning to base at RMH to perform ECR (blue). The percentage of suburbs in which MSU is superior to usual ambulance is displayed on the right-hand side. If the hospital can reduce door to TPA from 60 to 40 min by usual ambulance route, then MSU can reach 60.1% of metropolitan Melbourne for TPA.

In these simulations we had empirically set door to needle time at 60 min (including time for performing advanced imaging studies such as CT Perfusion and CT Angiography). We do not have access to individual site's door to needle time metric. We have provided a widget under the tab Usual Ambulance so that the user can explore the data. The data shows that when the door to needle time is 45 min by usual ambulance route, MSU is superior in 99.5% of suburbs for tPA, 83.1% of suburbs for ECR at base and 97.3% of suburbs for ECR at base and MMC (**Figure 2**).

The use of telemedicine in MSU has been proposed in several studies (13, 18, 21). In a direct comparison between usual ambulance and MSU with telemedicine, the latter method results in earlier CT scan time (by 23 min) and TPA (by 39 min) (18). These studies have used scenarios played by actors and compare performance between on board neurologist and tele-neurologist (21). In these actor scenarios, there was no difference in time to TPA between on-board and tele-neurologists. Technical failure was reported in 2% of study employing actors for simulation (16) and deemed to be significant in 2% with "live" cases described by New Jersey group (13). In that study, **internet** reconnection was required in 39% (35/89) of cases. The Cleveland groups (18) did not described technical failure with telemedicine. Treatment of stroke mimics with telemedicine was estimated at ∼20% (13). This rate is comparable with the range of stroke mimics presenting to hospital. However, the time metric used in our study cannot evaluate this aspect.

Provision of telemedicine with modern CT Angiography or CT Perfusion add further complexity with transmission of data, not evaluated in earlier reports (13, 18, 21). We had optimistically set 15 min as the default Telemedicine consultation time and which include transfer of images from MSU back to base. In the absence of the on-board neurologist, transfer of images back to base is required both for clinical reading and clinical governance. Further, the default setting here for CT Perfusion is optimistic as there is time cost for processing of perfusion images for determining presence of salvageable tissue.

In this study, we have used a novel and objective computational method to map the service boundaries for MSU based on travel time to the hub. This work was based on similar strategies for mapping ECR boundary in Melbourne and Adelaide (12). The works performed here used software packages (*ggmap* and *leaflet)* within the R environment, due to our familiarity with these packages. These are not the only R packages that can used for geospatial works and interactive display of map. Other R packages for geospatial analysis include *googleway* (access Google Map API) and *taRifx.geo* (access Google and Bing Map API) (22)*;* and for map display, there is *plotGoogleMaps* package. Outside of R environment, investigators can use python (23), matlab (24), javascript, and java.

Our study has several limitations outline below. It can be criticized as giving unfair advantage to the MSU as most of the simulations in MSU were performed without CT Perfusion. By contrast, the Usual Ambulance has a CT Perfusion arm which add 10 min to the hospital processing time. When this 10 min advantage has been removed, the MSU approach is still superior for delivery of TPA in 99.5% of suburbs, provision of ECR at RMH base in 92.3% of suburbs and provision of ECR at RMH or MMC in 98.4% of suburbs. The reader can click on the tab Model for Usual Ambulance and adjust the widget "Time (min) to process patient at hospital for TPA after arrival-usual ambulance." The app can be construed as simplistic in its focus on superiority of one model over another in terms of alarm to reperfusion therapy time and not focus on other aspect decision on reperfusion such as clinical variables, LVO status and angiographic suite availability. In this study we had made the assumption that availability of angiographic suite is high given that designated ECR hub in Melbourne are required to have two angiographic suites. This use of the app is different from that used by others for field triaging of stroke (25). We had performed the modeling with RMH as base of MSU for strategic planning and modeling. We did not analyze the possibilities of MSU being at different locations around Melbourne. With the 76 min radius, the MSU can cover metropolitan Melbourne easily and respond to call on the West side of Melbourne after delivering care in the East side. We had explored this possibility by interrogating Google Map API during peak hour traffic and found the traveling time was within the 76 min.

The app was developed focused on time metric for defining operating characteristics of MSU from alarm to reperfusion therapy time. However, MSU has other benefit including its use in field triaging of hospital destination for definitive therapy when the MSU is combined with CTA. In this role it can be combined with non-MSU ambulance to take the patient to the destination and the MSU can proceed to the next stroke code. This role of MSU for field triaging of therapy cannot easily be provided by using CT only. Finally, the app was intended for strategic decision making about the operating characteristic of the MSU. It can be modified for day to day analysis if needed. We have provided the source code on github account for anyone wishing to make changes (https://github.com/GNtem2/AmbMC).

In this study we proposed that the travel time from Google Map API were similar to that observed when traveling on ambulance. In our previous analysis, we had found this the difference between the travel time is in order of min (12). One drawback of this study is that it assumes that time cost is the main consideration when deciding hardware and software (CTA and CTP) or method of stroke diagnosis (on board neurologist or telemedicine). An earlier study had used data from meta-analysis of TPA to project cost benefit ratio with MSU (26). Other study described cost relating to purchase and maintenance of connectivity devices for telemedicine (13). There are current attempts data for cost effectiveness analysis and hopefully these papers will be available in the near future (11). An additional variable is sustainability of the work force and which depends on the number of stroke (vascular) neurologist available work on-board MSU (27).

In summary, we have provided a data driven approach to determine the operating parameters as well as location of base of MSU. Our recommendation is that MSU can be performed with CT Angiography, if the intention is to use MSU to triage site for ECR. The use of CT Perfusion and Telemedicine require further consideration and planning. This recommendation would change in the future as technology improves and acquisition and processing time can be significantly reduced. This approach can be used where Google Map API is available.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

TP and HM: design and concept; TP and RB: coding and data analysis; TP, RB, HM, VS, MP, HZ, SD, and GD: writing.

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frontiers in Neurology

ORIGINAL RESEARCH
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Googling Location for Operating Base of Mobile Stroke Unit in Metropolitan Sydney

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Background and purpose: The recent advances in stroke therapy have placed focus on delivering care within the first hour after stroke onset (golden hour), principally through the use of Mobile Stroke Unit (MSU) to bring the hospital to the patient. The aim of this project is to search the location of MSU hub in Sydney, Australia, optimizing for catchment, transport to nearest thrombolysis and endovascular clot retrieval (ECR)/thrombectomy capable hospital and population at risk.

Methods: Traveling time was performed using *ggmap* package in R to interface with Google Maps application program interface (API). This analysis estimates the travel time from the centroids of each suburbs to five potential MSU hubs (Royal Prince Alfred, Prince of Wales, Royal North Shore, Liverpool, and Westmead hospitals) and eight thrombolysis capable hospitals. It is proposed that the MSU should be deployed at ECR hub to cover the suburbs, not well-covered by thrombolysis and ECR capable hospitals. This step was performed by assigning membership to hospitals within 30 min traveling time to the ECR hub. The base hub of the MSU was proposed as the closest hub (providing ECR) to the least well-served suburbs. The population serviceable by MSU was estimated using stroke incidence studies in Melbourne and Adelaide.

Results: The largest population, serviceable by MSU within 30 min (4,606 cases), 45 min radius (8,918 cases), and 60 min (10,084 cases), was Royal North Shore followed by Royal Prince Alfred, Liverpool, Westmead, and Prince of Wales hospitals. Prince of Wales hospital has the smallest catchment within 30 min (3,078 cases), 45 min (7,721 cases), and 60 min (9,984 cases). Suburbs at the edge of metropolitan Sydney such as the Northern Suburbs are less well-served by thrombolysis and ECR capable hospitals. There are 10 suburbs within 30 min travel of one hospital. The remainders are within 30 min of two or more hospitals.

Conclusions: Any of the five endovascular clot retrieval capable hospitals are capable of serving as a hub for MSU. We provide a method to identify the hub based on location of suburbs less well-served by other hospital.

Keywords: stroke, mobile stroke unit, optimization, google maps, endovascular clot retrieval

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INTRODUCTION

The recent advances in stroke therapy have placed focus on delivering care within the first hour after stroke onset (golden hour) (1). A potential solution is the use of Mobile Stroke Unit (MSU) to bring the hospital to the patient for providing thrombolysis. Since the publications of the endovascular clot retrieval hospital (ECR)/thrombectomy trials in 2015 (2–7), a new indication for MSU is to triage transportation of patients to the appropriate hospital for ECR. The first randomized trial in 2012 showed an absolute difference of 16 min (8); this had occurred in the context of the MSU operating only a short range from base (8). Subsequent publications showed a difference of 39 min in time to thrombolysis (9). The MSU is a modified ambulance, which sometimes approaches the size of a truck. It is equipped with CT scanner and a mobile pathology laboratory and staffed by ambulance officer, nurse, radiographer, and in some places, doctor. There is strong interest in developing this platform and a model currently exist in Melbourne, Australia's second largest city.

There are several models for operating MSU around the world (1). In one model, MSU is located in a central location in a fire station and travel up to 16 min from base (10). A health economic analysis in Germany suggested MSU can provide service up to 30 km radius from base (11). The model in Edmonton, Canada provides service in rural Alberta up to a radius of 250 km^2 (12). The varying operating radii of MSU suggest that its deployment has not been formally evaluated. In the Australian context, the Melbourne model operates MSU from a centrally located major hospital, Royal Melbourne Hospital, and travel a 20 km radius from 8 a.m. to 6 p.m. (13). This model had occurred at Royal Melbourne Hospital and was nominated as the first designated ECR hub in Melbourne (14). Subsequently, a geospatial optimization analysis suggested that such a model can operate up to 76 min from base (15). In another paper, in this special issue of Frontiers in Neurology, the role of MSU in performing triaging of patients for therapy in the rural setting was explored (16). In this study, we propose the use of *ggmap* interface to Google Maps API to assign the base for operating MSU in Sydney based on proximity of the hub to the suburbs less well-resourced in terms of closeness to hospitals providing ECR and thrombolysis (14). The optimization will be performed for catchment, transport to nearest thrombolysis-capable hospital, and population at risk of stroke. Sydney is the ideal site for this study, as the locations of the ECR hubs have not been finalized and all potential ECR hubs are eligible as the base (17).

METHODS

Setting

Sydney is the capital city of the state of New South Wales, Australia with a population of ∼5.1 million. The number of strokes has been estimated using the 2016 census data (1) for each age band and the stroke incidence study in Melbourne and Adelaide (18, 19). This study involves simulations (no patient data are used) and as such received a waiver from the Monash Health Human Research Ethics Committee.

ECR Capable Hospitals in Sydney

At present there is no official statewide protocol for ECR in Sydney (20). There are five hospitals (Royal Prince Alfred, Prince of Wales, Royal North Shore, Liverpool, and Westmead) capable of acting as ECR hubs. There is one ECR hub, located 159 km north of Sydney. Similar to the Melbourne model of basing the hub in a major teaching hospital, these hubs may serve as the base for MSU. In addition, there are eight hospitals providing thrombolysis service in metropolitan Sydney and eight outside of metropolitan Sydney (20).

Google Maps API

Estimation of ambulance travel times and potential hospital catchment were performed using the *ggmap* (21) (R Project for Statistical Computing, version 3.4.4) interface to the Google Maps Distance Matrix API. The transport time, from each hospital to each suburb centroid, was computed during peak morning traffic. Interactive web-based maps of the models were generated using *leaflet* (R package) with tiles from OpenStreetMap (©OpenStreetMap contributors; for copyright, see www.openstreetmap.org/copyright) (22).

Optimization

We formulated the problem as a variant of the maximum coverage (23). In a traditional maximum coverage problem, the hospital sites are not yet determined and the optimization is performed to allocate the sites, which provide best coverage for the area. In this case, the hospitals have been built and each have their own capabilities such as thrombolysis capable or ECR capable. We propose that the MSU should be deployed to cover the suburbs, not well-covered by thrombolysis and ECR capable hospitals. This step was performed by assigning membership to hospitals within 30 min (24). From an equitable point, the suburbs, which have least memberships, were considered to be more likely to benefit from MSU compared to suburbs with multiple memberships (25). The base hub of the MSU was proposed as the closest hub to the least well-served suburbs.

In addition, we provide a sensitivity analysis by estimating the population at risk of stroke serviced by MSU. This analysis was done by extending the base from 30 to 60 min (24).

RESULTS

The map (**Figure 1**) illustrates the suburbs, well-served by overlapping catchment of other hospitals. These are suburbs, located between the following Royal Prince Alfred, Westmead, Sydney Adventist, Bankstown, and St. George. Concord hospital is located at the center of these suburbs with overlapping catchment. By contrast, the suburbs at the edge of metropolitan Sydney such as the Northern Suburbs are less well-served by thrombolysis and ECR capable hospitals. On the map these Northern suburbs have values of one only, indicating that they are serviced by only 1 hospital. **Figure 2** is a histogram of the suburbs and their 30 min proximity to a thrombolysis and ECR capable hospitals. Ten suburbs are within reach of one hospital within 30 min and 200 suburbs are within reach of two or more hospitals within 30 min. Thirty suburbs are within

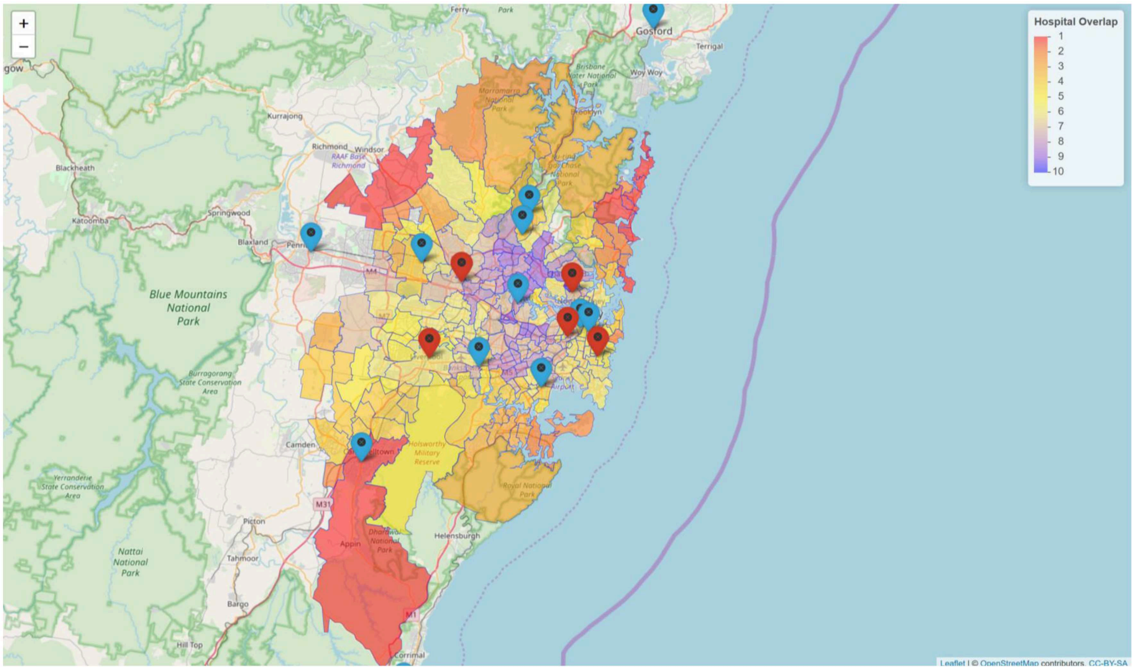

FIGURE 1 | Coverage of suburbs by thrombolysis and clot retrieval hospitals. There are five ECR capable hospitals (red icons) and eight thrombolysis capable hospitals (blue icon) in metropolitan Sydney. The red color polygon indicates less overlap and the purple color indicates high number of overlap.

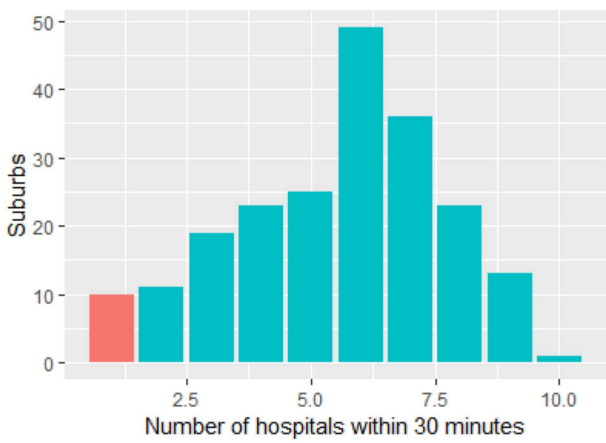

FIGURE 2 | Relationship between suburbs and hospital coverage in Sydney. There are 10 suburbs within 30 min travel of one hospital (red). The remainders are within 30 min of two or more hospitals.

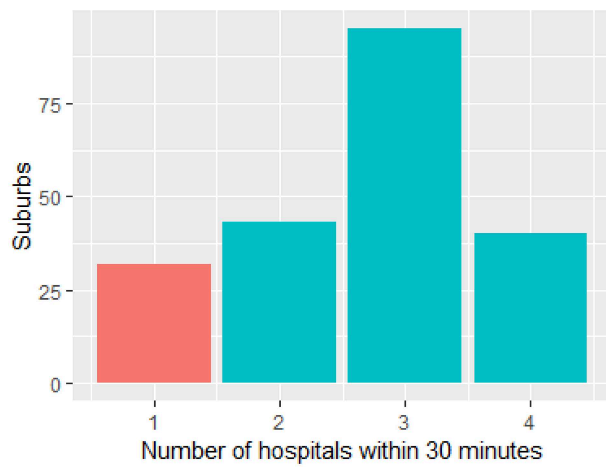

FIGURE 3 | Relationship between number of suburbs and coverage by ECR capable hospitals. Thirty-two suburbs are within 30 min of one ECR capable hospital (red). ECR, endovascular clot retrieval.

30 min of one ECR capable hospital. One hundred and thirty-five suburbs are within 30 min of more than three ECR capable hospitals (**Figure 3**).

The largest population, serviceable by MSU within 30 min (4,606 cases), 45 min radius (8,918 cases), and 60 min (10,084 cases), was by Royal North Shore hospital followed by Royal Prince Alfred, Liverpool, Westmead, and Prince of Wales hospitals (**Table 1**). Prince of Wales hospital has the smallest catchment within 30 min (3,078 cases), 45 min (7,721 cases), and 60 min (9,984 cases). Within 60 min from hub, five sites differ by 140 cases. Three of the sites have two associated spokes hospitals (**Table 2**; **Figure 1**).

DISCUSSION

In this study, we have used data driven method to map location of MSU base in Sydney using Google Maps API estimate of travel time from the ECR and thrombolysis capable hospitals. This issue

TABLE 1 | Projected number of patients with stroke serviced by different combinations of ECR hubs.

Hospital	Melbourne incidence *30 min	Melbourne incidence *45 min	Melbourne incidence *60 min	Melbourne incidence *20 km	Melbourne incidence *30 km	Melbourne incidence *50 km	Adelaide incidence #30 min	Adelaide incidence #45 min	Adelaide incidence #60 min	Adelaide incidence #20 km	Adelaide incidence #30 km	Adelaide incidence #50 km
RPA	4,247	8,475	10,047	4,717	7,541	9,944	2,465	4,911	5,824	2,736	4,367	5,762
LPH	3,772	8,475	10,047	2,986	6,121	9,143	2,198	4,337	5,519	1,738	3,558	5,306
WH	4,294	7,988	9,844	3,550	6,588	9,859	2,498	4,640	5,708	2,064	3,827	5,713
POW	3,078	7,721	9,984	2,874	5,836	9,424	1,784	4,468	5,788	1,666	3,376	5,453
RNS	4,606	8,918	10,084	3,650	6,497	9,349	2,665	5,164	5,845	2,117	3,759	5,410

*Melbourne stroke incident study. #Adelaide stroke incident study. ECR, endovascular clot retrieval; RPA, Royal Prince Alfred; WH, Westmead Hospital; POW, Prince of Wales Hospital; RNS, Royal North Shore Hospital.

TABLE 2 | Thrombolysis capable spoke hospital proximity to ECR hub.

Hospital	Spoke hospitals 1 (min)	Spoke hospitals 1 (km)	Spoke hospital 2 (min)	Spoke hospital 2 (km)
RPA	25.2	12.9		
LPH	17.1	10.7	26.0	28.5
WH	20.7	12.7	33.0	29.3
POW	24.4	16.1		
RNS	25.8	19.1	22.7*	16.4*

*Privately operated hospital. ECR, endovascular clot retrieval; RPA, Royal Prince Alfred; WH, Westmead Hospital; POW, Prince of Wales Hospital; RNS, Royal North Shore Hospital.

arises as there are five ECR capable hospitals in Sydney; each has their merits of operating as a base for MSU. Using the idea of equity, an ECR hub was identified as the one that was closest to the suburbs, least served by ECR and thrombolysis capable hospitals. Our methodological approach is of use when planning to invest in MSU.

The use of geographical information systems for health service design is evolving since 2017 (14, 15, 26–30). In this study, we have accessed Google Maps API for traffic data due to our familiarity with this platform (14, 15, 26–30). Use of Google Maps API for this purpose has been done in Australia and North America (14, 15). Those planning similar studies in other part of world such as Republic of Korea (South Korea) would need to access to Daum, Naver, or VWorld Map API. In People's Republic of China, Baidu Map API is preferred to Google Maps API. These tools can be combined with *ggmap* or other tools discussed in this special issue of *Frontiers in Neurology (Stroke)*. In the Republic of China (Taiwan), Google Maps API is available for travel time estimation.

The approach we have taken for evaluating MSU base in Sydney is different from that in Melbourne (15). The MSU base in Melbourne has already been chosen and stroke neurologists and nurses from Royal Melbourne Hospital form part of the crew for the MSU (30). The objective of the paper is to ascertain the range of the MSU in Melbourne as the original intention was to restrict its operation to just 20 km from base. Our approach shows that in Melbourne, MSU can operate as far as 76 min from base and would provide superior time with respect to administration of TPA (31). With the range of operation in mind, it is proposed that provision of MSU service to an area, well-served by multiple adjacent hospitals, would not be equitable. The alternative argument is that MSU provides a mean to reduce door-in to door-out time, even within these well-covered suburbs. The argument would be that even among suburbs, well-served by other hospitals, there is still the issue of door-in to door-out time, which can vary from 85 min in Rhode Island (32) to 106 min in Melbourne (31).

It is possible that the issue of deciding between thrombolysis and ECR capable hospitals and MSU in a well-service catchment has not been explored in detail, as some of the centers operating MSU have only one ECR hub and have a small catchment population. Sites such as Lucas County serves a population of 433,689 (33); New Jersey model serves a modest population of 460,000 (34); and the Cleveland model serves a population of 390,000 (35). In Germany, there is exploration on the deployment of MSU in rural areas (16). In Edmonton, Canada, there is extension of the operating radius as far as 250 km from base (12).

Similar to the Houston and Melbourne model of basing the MSU hub in a major public teaching hospital (36), the rationale for the use of major hospital is that a stroke neurologist or neurology trainee from that hospital participates in the team. This has been the case for the first 2 years in Houston (36). This approach is different from the original model in Berlin in which the base is in a centrally located fire station in Berlin. If the desire is to locate the base in a central location, then the choice would be Royal Prince Alfred hospital, which is closest to the center of Sydney. However, such a model would be less equitable, given the number of suburbs, serviced by other hospitals. A counter argument would be that the suburbs with service by multiple hospitals is that where people live with risk of stroke.

Projection of patients at risk of stroke is based on stroke incidence studies from Melbourne (on the East coast of Australia) and Adelaide (on the South Coast of Australia) (18, 19). The studies were performed 13 years apart with the latter study from Adelaide documenting a much lower stroke incidence. The improved stroke incidence can be due to different methodology or improved stroke prevention strategy. As such we have provided data on the estimated number of stroke cases using stroke incidence both studies.

A limitation of this study is that it is based on simulations and not observed cases of stroke. We had circumvented this by simulating stroke cases in the centroid of each suburb. This approach provides an average of the trip time. Another limitation in the proposal for MSU is the issue of cost effectiveness, which has not yet been done. Current studies are underway on cost effectiveness of analyses of MSU (37, 38). A critical issue for cost effectiveness is the requirement to demonstrate difference in primary outcome on disability; so far the trial confirmed reduction in time to give thrombolysis only (9). The findings with reduction in time to thrombolysis are consistent whether in Europe or North America (35). However, this study has not focused on clinical outcome. The flow chart from this study shows another issue while constructing the cost effectiveness analysis (35). Twenty eight of 100 patients, treated by MSU, did not have stroke and 30 were classified as possible acute ischemic stroke. A further 217 trips (out of total 317 trips) were canceled prior to MSU arrival in this Cleveland Clinic study (35).

Depending on the configuration of MSU, the cost has been estimated to be around US$750,000 to US$1,400,000. The running cost of operating MSU during office hour is estimated to be around US$1,000,000 (34). Recently, a group in Lucas County Ohio reported on their initial experience with operating MSU 24 h a day (33). Data on 24-h operation and cost effectiveness study such as these will help inform the need for MSU.

This study was not designed to address the issue of cost effectiveness or propose the purchase of MSU but rather to evaluate the location for deployment of MSU. In the process of performing these analyses, there were issues on clustering or proximity of hospitals with thrombolysis and ECR capability. There may be a need to allocate resources equitably from inner Sydney to outer Sydney while planning the location of MSU hub. This is an issue that is not unique to Australia but is also relevant in Europe (16) and Canada (12). In London, this had been addressed by reducing the number of hospitals providing thrombolysis service (24, 39). The model was designed in such a way that no Londoner should be more than 30 min away from a hyperacute stroke service (24). A recent analysis on the effect of centralizing and rationalizing of stroke service in two metropolitan cities in England shows that the changes result in improved outcome (length of stay and mortality) and are sustainable (40). These centralized stroke services are configured for thrombolytic therapy and works are underway to examine implementation of ECR (41). It is not clear if this process would result in further reduction in hospitals providing thrombolysis and ECR. Decisions on the number of ECR and thrombolysis capable hospitals serving Sydney would need to be made before deciding on base for MSU.

In summary, any of the ECR-capable hospital can serve as a hub for MSU. We provide a method to identify the hub based on location of suburbs less well-served by other hospital.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

TP: design, analysis, and writing the manuscript. RB, VS, and HM: writing the manuscript.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Planning and Providing Acute Stroke Care in England: The Effect of Planning Footprint Size

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Background: Guidelines in England recommend that hyperacute stroke units (HASUs) should have a minimum of 600 confirmed stroke admissions per year in order to sustain expert consultant-led services, and that travel time for patients should ideally be 30 min or less. Currently, 61% of stroke patients attend a unit with at least 600 admissions per year and 56% attend such a unit and have a travel time of no more than 30 min.

Objective: We have sought to understand how varying the planning and provision footprint in England affects access to care whilst achieving the recommended admission numbers for hyper-acute stroke care. We have compared two different planning footprints to national-level planning: planning using five NHS Regions in England, and planning using 44 Sustainability and Transformation Partnerships (STPs) in England.

Methods: Computer modeling and optimization using a multi-objective genetic algorithm.

Results: The number of stroke admissions between STPs varies by seven-fold, while the number of stroke admissions between NHS Regions varies by 2.5-fold. In order to meet stroke admission guidelines (600/year) for all units the maximum possible proportion of patients within 30 min would be 82, 78, and 72% with no boundaries to planning/provision, NHS Region boundaries, and STP boundaries (in these scenarios patients cannot move outside of their own STP or NHS Region). If STP or NHS Region boundaries are removed for provision of service (after planning is performed at these local levels), travel time is improved, but number of admissions to individual hospitals become significantly changed, especially at STP planning level where admission numbers per unit changed by an average of 204 (19%), and not all units maintained 600 admissions after removal of boundaries.

Conclusion: Planning and providing services at STP level could lead to sub-optimal service provision compared with using larger and more consistently populated planning areas.

Keywords: stroke, health services research, health service planning, thrombolysis, genetic algorithm

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INTRODUCTION

Stroke is a major cause of burden on individuals and healthcare services. It was estimated that in 2010, there were 5.9 million deaths and 33 million stroke survivors (1). Eighty five thousand people are hospitalized with stroke each year in England, Wales and Northern Ireland (2). Over the last 25 years stroke was the leading cause of lost disability-adjusted life years, which combine mortality and disability burdens (3).

Centralization of stroke care in London, into large hyperacute stroke units (HASUs), where care is delivered by specialist stroke teams, has been shown to reduce mortality, reduce length of stay, increase thrombolysis rates and reduce long-term costs to the NHS (4, 5). As a consequence of these improved outcomes and reduced costs, the NHS in England has promoted the reconfiguration of stroke services across England with the aim that all stroke care is delivered in HASUs (6).

For acute stroke units, national guidelines recommend that each HASU should have at least 600 confirmed stroke admissions per year (7), with a recommendation that travel time should ideally be 30 min or less, and no more than 60 min (8).

The English NHS is facing increasing demand, bringing with it the need to continually improve and transform services. In 2015, NHS England, the statutory agency responsible for the provision of healthcare in England, announced 44 geographical areas that would build "Sustainability and Transformation Plans" (subsequently Partnerships; STPs, with some evolving into "Integrated Care Systems") to deliver sustainable transformation in health and care outcomes between 2016 and 2021 (9, 10). STPs are a key footprint for planning of many acute services in England. In addition to STPs there are five NHS Regional teams which provide additional support and leadership in commissioning services. Each STP is assigned to one of the five regions.

We have previously described the use of a genetic algorithm to optimize the planning of the number and locations of acute stroke services (thrombolysis and thrombectomy) in order to maximize the proportion of patients with good access whilst meeting guidelines for the number of admissions (11, 12). In previous work we assumed no hard borders to planning or service provision. In this paper we investigate the effect of applying hard borders to planning provision, either around the five NHS Regions or the 44 STPs. We investigate how well a boarders system can perform compared to a border-less system, and we look at the effect of planning assuming borders but those borders then being ignored for provision of care.

We focus on HASUs providing thrombolysis as those are expected be the first point of access for acute stroke care.

METHODS

All data and optimization code used are available (see section Data Availability below). Detailed methodology is available in an on-line **Appendix** in Supplementary Material.

Detailed methodology has also previously been described (11).

Data

Location data used Lower Super Output Areas (LSOA) across England. LSOAs are geographic areas with a population of ∼1,500 and with an average distance of 2 km between nearest-neighbor LSOAs. There are 32,844 LSOAs in England, though we exclude the Isles of Scilly in this analysis. The home location of the person was taken as the population-weighted centroid of each LSOA (13). Travel times were based on the estimated fastest road travel times from the postcode closest to the population-weighted centroid of the parent LSOA to the postcode of the HASU. Travel times were estimated using Maptitude (www.maptittude.com) and MPMileCharter (http://www.milecharter.com) for normal road conditions without significant congestion.

Admissions for stroke per LSOA for 3 years 2014–2016 were obtained from NHS Hospital Episodes Statistics managed through Lightfoot Solutions (www.lightfootsolutions.com). We included 242,874 patients coded with an emergency admission of ischaemic or hemorrhagic stroke (primary diagnosis ICD-10 I61, I63, I64). Admission numbers per institution were obtained from the 2015/16 Sentinel Stroke National Audit Programme (SSNAP) for admissions (2). The location of 127 acutely admitting stroke units was taken from the 2016 SSNAP annual report (2).

Figure 1 shows the geographical boundaries of STPs and NHS Regions.

Optimizing Choice of Locations of Units

The model predicts, for any configuration of HASUs, the number of admissions to each HASU and the travel time from the patient's home to their closest (by travel time) HASU.

We used a bespoke genetic algorithm based on NSGA-II (14) to identify potential configurations of HASUs across England, balancing the competing objectives of access (travel time) and sustainability of expert services (admission numbers). We include any unit offering hyper-acute care (which will always include ability to treat with thrombolysis; units also offering thrombectomy are also considered HASUs for the purpose of this modeling).

In the algorithm, each solution is coded as binary array—with each element of that array corresponding to an existing stroke unit. A zero indicates that the unit is not selected to be a HASU, and 1 indicates that a unit is selected to be a HASU. The algorithm maintains a population of such solutions (typically, but not always, 10,000 solutions at any given time).These solutions go through a series of generations (typically 300–500). In each generation two existing solutions are selected and hybridized (with occasional random mutation). This is repeated until the "child" population (the new solutions) is as large as the "parent" population (the existing solutions). The two populations are combined and the best solutions are kept. For selection of best solutions we used a "pareto-based" method. Pareto selection is designed to capture all solutions that offer the best trade-off between competing multiple objectives. Solutions are eliminated if another solution is equally as good in all optimization parameters and is better in at least one parameter. The population may then be trimmed if necessary using "crowding distances" (where solutions that are very similar in results to others are more

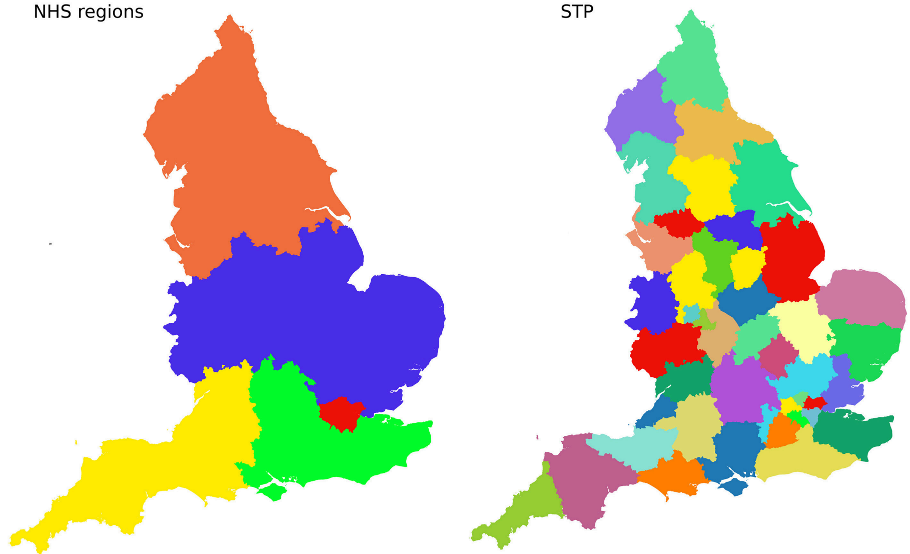

FIGURE 1 | Boundaries of 5 NHS Regions **(Left)**, and 44 Sustainability and Transformation Partnerships (STPs, **Right**).

likely to be removed), or may be further expanded by repeating the pareto-selection process for the hitherto unselected solutions.

The selected configurations were based on a range of optimization parameters which seek to minimize travel times and to control admission numbers. These parameters were (1) number of HASUs (lower is better), (2) average travel time (lower is better), (3) maximum travel time (lower is better), (4) proportion of patients with a travel time of no more than 30 min (higher is better), (5) lowest number of admissions to any HASU (higher is better), (6) greatest number of admissions to any HASU (lower is better), (7) proportion of patients attending a HASU with at least 600 admissions per year (higher is better), (8) proportion of patients with a travel time of no more than 30 min and attending a HASU with at least 600 admissions per year (higher is better).

The algorithm was run assuming no boarders (patients may attend their closest HASU), or assuming patients may only attend a HASU within their own STP or NHS Region. Additional analysis was performed whereby solutions chosen assuming boarders were present, were then evaluated for performance if those boarders are then ignored for service delivery (patients may attend their closest HASU regardless of STP or NHS Region).

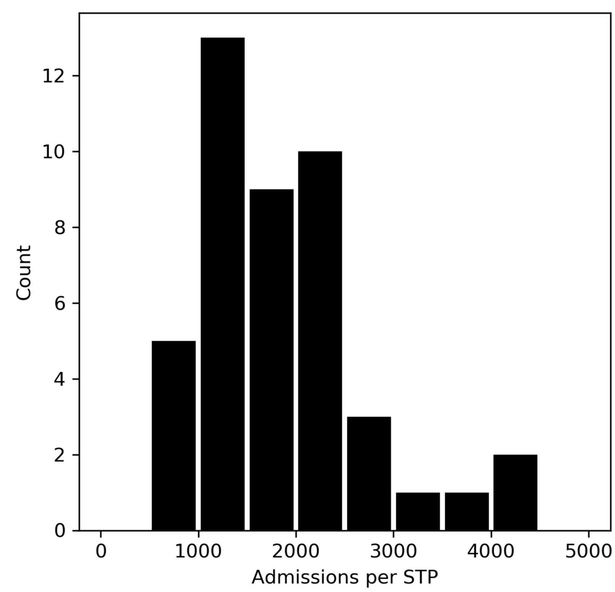

FIGURE 2 | The number of stroke admissions per year by STP home location of patient. The x-axis shows admission numbers per STP in 500 admission bins, and the y-axis shows the count of STPs with that admission bin range.

RESULTS

Stroke admissions per STP ranged from 621 to 4,421 per year (**Figure 2**), a seven-fold range. Admissions per NHS Region range from 9,092 to 25,445.

The trade-off between achieving target admissions and target travel times are shown in **Figure 3**. These results assume that both planning and provision have hard boundaries (that is each region plans and provides for only their own constituents). Increasing the number of HASUs increases the proportion of patients within 30 min, however increasing the number of HASUs above about 80 leads to a decreasing proportion of patients being treated in units with at least 600 stroke admissions per year. The maximum proportion of patients attending HASUs that are both within 30 min and admit at least 600 stroke patients per year occurs at 70–90 HASUs nationally.

As planning footprint is reduced in size (from national, to NHS Regions, to STP) the ability to meet both target travel

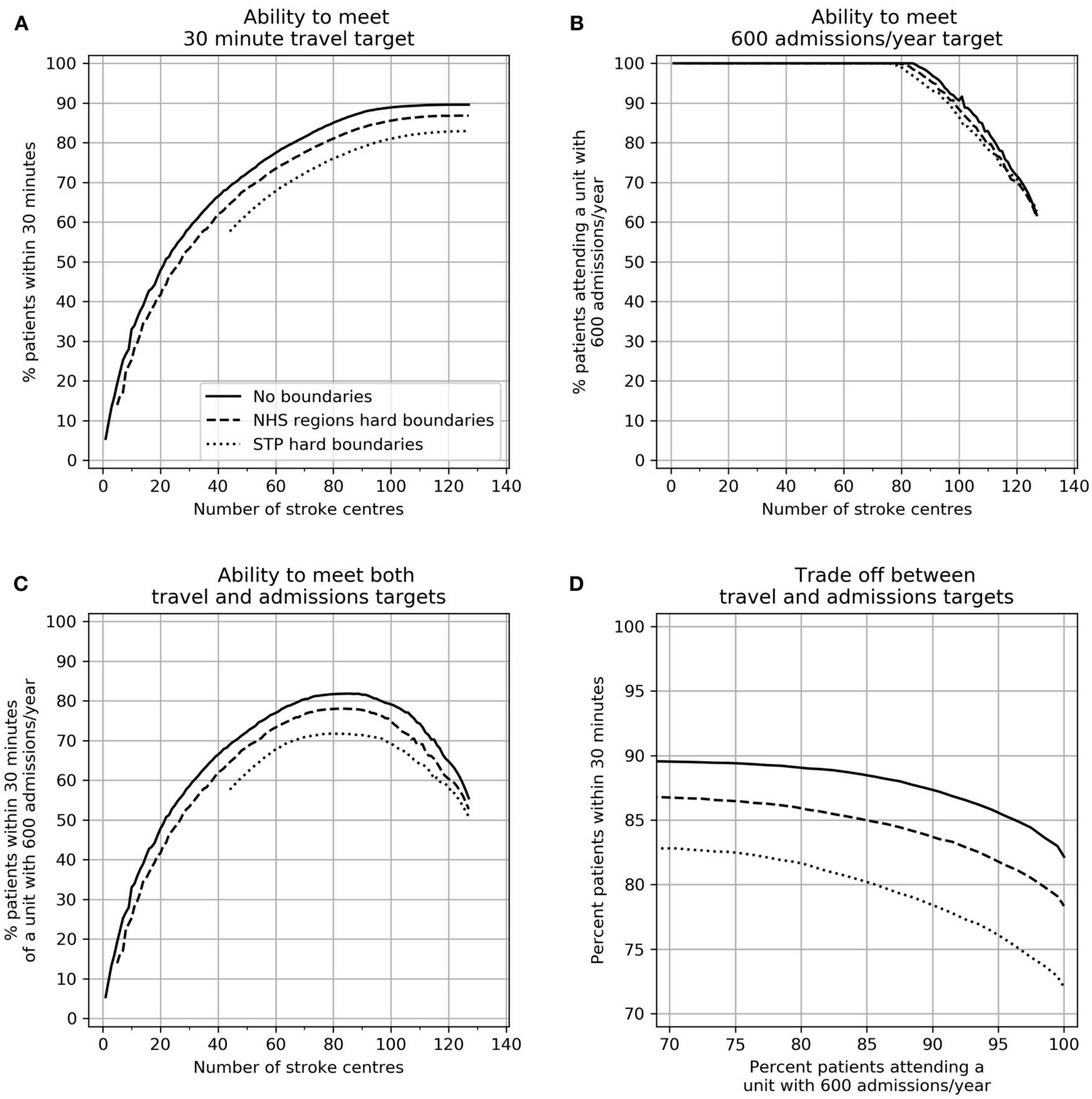

FIGURE 3 | The effect of changing the number of HASUs and the planning footprint size on **(A)** the ability to provide 30 min access to HASUs, **(B)** the ability to meet a 600 admissions/year target, **(C)** the ability to meet both access and unit size targets, and **(D)** the best achievable compromise (Pareto front) between access and unit size targets. In all plots the solid line represents no boundaries, the dashed line restricts patients to NHS Region boundaries, and the dotted line restrict patients to STP boundaries.

times and target admissions is compromised, though the effect on travel time is more pronounced. At all points the best achievable compromise between maximizing access (greatest number of patients within 30 min) and maximizing the number of patients attending a HASU with 600 admissions is compromised by planning within local or regional boundaries.

In order to meet stroke admission guidelines for all HASUs (600/year) the maximum possible proportion of patients within 30 min would be 82, 78, and 72% with no boundaries to planning/provision, NHS Region boundaries, and STP boundaries. The best achievable 95th percentile travel times would be 46, 47, and 55 min. To achieve this there would be 84, 79, or 76 HASUs for the three planning footprints.

We examined the effect on travel times and admission numbers if planning were performed at NHS Region or STP level, but then patients attended the closest HASU regardless of boundaries (closest by travel time). For these models we selected configurations that maximized the proportion of patients attending a HASU with target admission numbers, then selected configurations with the lowest maximum admission numbers (to control the size of the largest units), and then selected from those the configuration which maximized the proportion of people within 30 min of their closest planned HASU.

These configurations had either 76 HASUs (optimization based on STPs) or 77 HASUs (optimization based on NHS Regions).

When people attend their closest HASU regardless of boundaries, travel times are improved, compared with the original planned configuration assuming people stay within STPs or NHS Regions. When planning at NHS Region or STP level the proportion of patients within 30 min increased from 72–76 to 79% (for both planning levels). There is, however, significant disruption to admission numbers (**Figure 4**). When *planning* at STP level, assuming a contained population within a STP, but with *provision* then occurring without boundaries to people, admission numbers per HASU changed by an average of 204 (19%), and the number of HASUs achieving target admissions fell from 76 (all HASUs) to 73. The effect of planning at NHS Region level, but with patients then attending their closest HASU regardless of boundaries had significantly less effect. Admission numbers per HASU change by an average of 69 (7%), and all HASUs maintain the target 600 admissions per year.

DISCUSSION

Providing good access times to acute hospital services for the whole population necessarily requires a large number of hospitals. In contrast, providing 24/7 consultant-led services for time-critical emergency services (such as those for stroke) requires limits to be placed on the number of providers in order for each hospital to maintain target admissions required to sustain a specialist service that operates 24/7. These two objectives will always conflict, requiring careful judgement of the best balance between them. Computer modeling can help achieve a better, more quantitative, understanding of the trade-off between these conflicting objectives.

Currently, a little more than half of stroke patients attend a HASU with greater than the recommended 600 admissions per year; In 2015/16 61% of acute stroke admissions attended a HASU with at least 600 confirmed stroke admissions per year (2), with the largest unit having 2,001 admissions. Fifty out of 130 HASUs had at least 600 admissions per year. Fifty six percent of patients

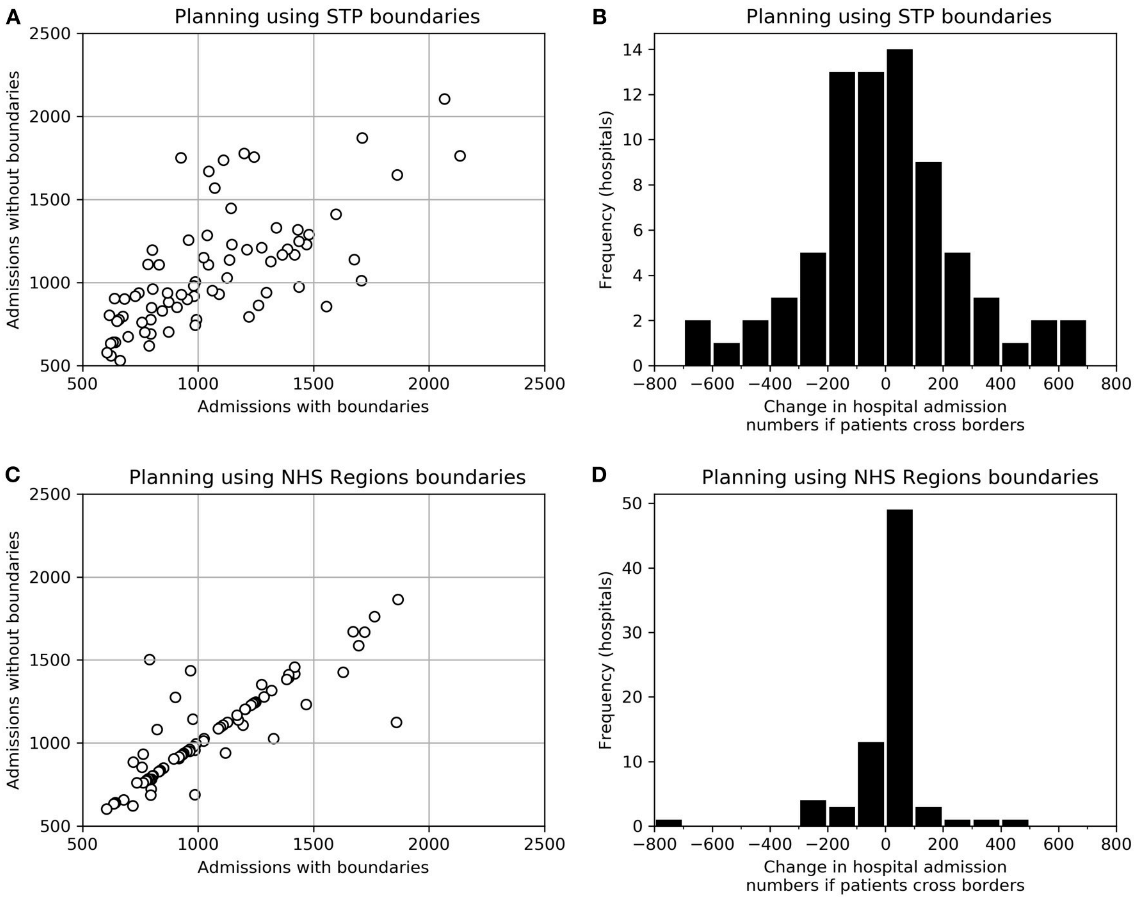

FIGURE 4 | The effect of planning access to acute stroke services using STP or NHS Region boundaries, but then providing access without regard to boundaries. **(A)** Admission numbers to each HASU as originally optimized using STP boundaries, and admission numbers to the same HASUs if no boundaries are applied when providing care. **(B)** A histogram of the change in admission numbers between those expected when planning using STP boundaries and those expected if boundaries are ignored when providing care. **(C)** Admission numbers to each HASU as originally optimized using NHS Region boundaries, and admission numbers to the same HASUs if no boundaries are applied when providing care. **(D)** A histogram of the change in admission numbers between those expected when planning using NHS Region boundaries and those expected if boundaries are ignored when providing care.

attend a unit with at least 600 admissions per year and have a travel time of no more than 30 min. Our modeling has previously suggested that the proportion of patients attending larger HASUs may be significantly increased with relatively minor changes to access times (11). However, the extended modeling described here suggests that achieving better access to larger HASUs is compromised if small geographical areas, such as STP footprints, are used to plan and provide these services. The main effect is on travel times; if patients cannot cross STP boundaries then they may be forced to travel further to a HASU.

Target travel times and minimum admission numbers can only ever be a guide. They may, however, help understand the nature and extent of the trade-offs required where it is not possible to achieve both objectives simultaneously. Modeling may help inform decision making by clarifying and quantifying those trade-offs.

A further challenge for organizing acute healthcare by STP footprint is the large variation in the number of people in STP areas, with the largest STP having seven times more admissions, than the smallest.

Though planning may occur at local STP level it is highly possible that those boundaries become ignored for provision, especially when considering where to take emergency stroke patients. The resulting discrepancy between planning footprint and the realities of provision is likely to make regional planning less accurate than it could be, especially concerning estimations of admission numbers, and also lead to a choice of service configurations that is ultimately sub-optimal both for patient travel times and for the ability to maintain target admissions required to sustain expert 24/7 services.

We have previously published work on optimizing access to thrombectomy services (12). A conclusion was that a sustainable and accessible acute stroke service will require a drip-and-ship approach, where patients first attend their closest HASU where they would have access to thrombolysis. They would then be transferred to a thrombectomy center if they were thought suitable and their most local acute stroke unit did not provide it. As it is the local acute stroke center that will be the first access point for stroke services we have focussed our work on the effect of regionalization on that first access point, that of the local hyper-acute stroke unit providing thrombolysis.

In this paper we have focussed on acute stroke care in England. The principles and methodology should be directly applicable to many other countries as well. Key principles are (1) to use a methodology that fully explores the range of compromises between time to access services, and the ability of those services to sustain 24/7 expert care, and (2) understand how regionalization of planning might be compromising performance of the system as a whole. The methods and code published may be directly transferred to other countries.

CONCLUSIONS

Achieving best access times to acute hospital services for the whole population conflicts with the objective of reaching the minimum number of admissions in each type of unit required to provide good 24/7 consultant-led care for emergency or unplanned admissions. As the size of the geographical footprint for planning and provision is reduced to the level of STPs, the ability to meet access and admission targets becomes increasingly compromised, and the ability to predict admission numbers may be hampered by planning boundaries being ignored in practice. Planning and providing services at STP level could lead to sub-optimal service provision compared with using larger and more consistently populated planning areas.

Though we have focused on stroke care in England, the principles and methodology should be directly applicable to many other countries as well. Key principles are (1) to use a methodology that fully explores the range of compromises between time to access services, and the ability of those services to sustain 24/7 expert care, and (2) understand how regionalization of planning might be compromising performance of the system as a whole.

DATA AVAILABILITY

All data, raw results, and optimization code used are available from the following repository: https://github.com/MichaelAllen1966/1807_acute_healthcare_location_effect_of_boundaries. The code runs in Python 3.6 (or higher), a free and open source programming language (see www.anaconda.com for a commonly used installation of Python complete with scientific libraries).

AUTHOR CONTRIBUTIONS

MA conceived the original research plan, contributed significantly to writing the optimization and analysis code, and wrote the first draft of the paper. KP contributed significantly to the writing of the optimization and analysis code and contributed amendments to the paper. EV wrote the original optimization code, and was the primary author of the technical description (**Appendix** in Supplementary Material). MJ has provided clinical oversight to the project, and contributed to the aims of the project, interpretation of results and writing of the paper. KS had overall oversight of the work and contributed to the aims of the project, interpretation of results, and writing of the paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00150/full#supplementary-material

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CODE STROKE ALERT—Concept and Development of a Novel Open-Source Platform to Streamline Acute Stroke Management

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Introduction: Effective, time-critical intervention in acute stroke is crucial to mitigate mortality rate and morbidity, but delivery of reperfusion treatments is often hampered by pre-, in-, or inter-hospital system level delays. Disjointed, repetitive, and inefficient communication is a consistent contributor to avoidable treatment delay. In the era of rapid reperfusion therapy for ischemic stroke, there is a need for a communication system to synchronize the flow of clinical information across the entire stroke journey.

Material/Methods: A multi-disciplinary development team designed an electronic communications platform, integrated between web browsers and a mobile application, to link all relevant members of the stroke treatment pathway. The platform uses tiered notifications, geotagging, incorporates multiple clinical score calculators, and is compliant with security regulations. The system safely saves relevant information for audit and research.

Results: Code Stroke Alert is a platform that can be accessed by emergency medical services (EMS) and hospital staff, coordinating the flow of information during acute stroke care, reducing duplication, and error in clinical information handover. Electronic data logs provide an auditable trail of relevant quality improvement metrics, facilitating quality improvement, and research.

Discussion: Code Stroke Alert will be freely available to health networks globally. The open-source nature of the software offers valuable potential for future development of plug-ins and add-ons, based on individual institutional needs. Prospective, multi-site implementation, and measurement of clinical impact are underway.

Keywords: endovascular clot retrieval, stroke, open-source, communication platform, geotagging, mechanical thrombectomy

INTRODUCTION

Gold standard treatment of acute ischemic stroke relies on timely reperfusion of ischemic cerebral tissue. The two primary methods of reperfusion are thrombolysis using intravenous tissue plasminogen activator (IV tPA) and mechanical thrombectomy. These therapies have been proven to be effective in several randomized clinical trials and meta-analyses (1–3). With rapid reperfusion therapy, up to 70% of patients may have good neurological recovery (4).

Mechanical thrombectomy is superior to IV tPA for acute ischaemic stroke due to large vessel occlusion (LVO). In multiple recent trials, the effect of time to reperfusion with mechanical thrombectomy was directly proportional to patient outcome (5–7). It is estimated that every 1-min reduction in the interval between stroke onset and start of mechanical thrombectomy results in an additional week of healthy living (8).

A comprehensive stroke service is necessarily complex, involving medical professionals across multiple disciplines and departments. Such an intricate system is prone to inefficiencies related to delayed dissemination of information, communication duplication, and error as well as the need for consensus decision making among stroke specialists and neuro-interventionalists (NI). The time critical nature of cerebral reperfusion is a compelling motivation to optimize communication systems, allowing for synchronization and improved coordination of clinical information (9).

To address this need, we aimed to develop a novel, open-source, multi-platform communication application, named "Code Stroke Alert," that facilitates efficient multi-cast, tiered communication during the hyperacute management stages of an ischaemic stroke.

Stroke Pathway and Barriers to Timely Reperfusion

The basic pathway of communication in a stroke patient is outlined in **Figure 1**. Most strokes occur in the community and rely on initial recognition by the patient or a family member with subsequent first medical contact with local emergency medical services (EMS). Pre-hospital triage and care varies based on locality but generally involves a basic assessment by trained paramedics and transfer to a local stroke centre. The emergency department (ED) then alerts the radiology and stroke staff of the impending stroke (in most hospitals this is achieved through a group page). Much of the communication to this point is one-way, with limited ability to provide confirmation by any party, nor detailed clinical information.

On arrival to hospital, multiple processes happen quickly and simultaneously. The stroke patient will be reassessed in detail by ED nurses, physicians, and the stroke team, whilst simultaneous handover is provided by the paramedics. Throughout this period, there is constant communication between all parties and senior clinical decision makers within the team. Following clinical assessment, the patient will proceed to neuroimaging with computed tomography (CT). Based on imaging findings in correlation with clinical assessment, a treatment decision will then be made. If the decision is for mechanical thrombectomy, activation of the angiography lab and anesthetics team must occur immediately, with broader notification (stroke unit and admission logistics) shortly after commencement of the procedure.

There are a number of points in this complex process which are vulnerable to delay (**Table 1**). The initial recognition by community members is the first and there are concerted efforts being made to improve health literacy to address this issue. Once EMS have been contacted there is a triage and dispatch process and then time spent in assessment and information gathering. A decision has to be made regarding destination, followed by transport time to the target hospital. Within the hospital environment there is a further complex succession of medical assessment, imaging acquisition, decision-making and treatment, and in some cases, transfer to a mechanical thrombectomy-capable service may be required.

Up to 40 different health care professionals may be involved in this entire process for an individual stroke presentation. This includes, but is not limited to, paramedic staff, ambulance staff, emergency staff, stroke physicians, stroke nurses, radiologists, radiographers, radiology nurses, NI, anesthetics staff, orderlies, junior medical staff, and administrative staff.

Reliable and efficient communication is a necessity in such a scenario, but most hospitals currently rely on paging systems or paper information sheets with multiple handovers and a sequential dissemination of information. This can lead to communication duplication, information loss, security concerns and, ultimately, time delays. The bold text delays presented in **Table 1** highlight points at which we hypothesized that a dedicated, electronic information gathering and distribution program could accelerate the pathway of a stroke patient.

METHODS

Application Development

The Code Stroke Alert development team consists of a software engineer, a stroke neurologist, NI, a policy advisor, diagnostic neuroradiologists, a neurovascular stroke nurse practitioner, junior medical doctors, and medical students. All team members are volunteers who work collaboratively on different aspects of Code Stroke Alert based on their expertise. Code Stroke Alert development formally commenced in September 2017.

Development of the Electronic Platform

Given the wide range of healthcare professionals for whom the electronic communications platform is intended, the application has been written and developed by a multi-disciplinary team so that the priorities of each specialty are represented in the application and that user experience is logical and practical. The software developers have a background in healthcare or have experience in developing healthcare-related applications, including familiarity with the Health Insurance Portability and

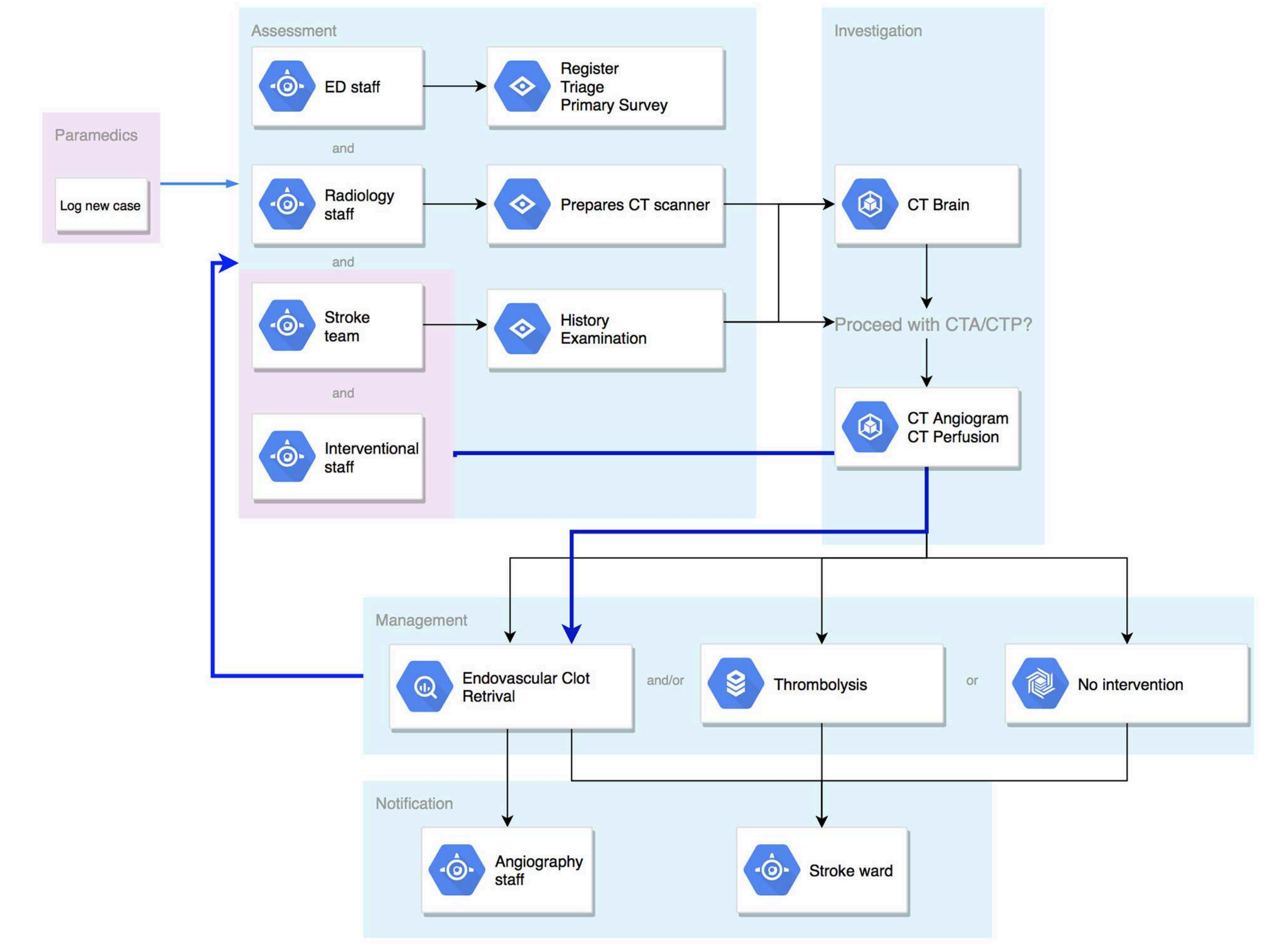

FIGURE 1 | Flowchart of communication pathway in a stroke case.

Accountability Act (HIPAA) and importance of privacy with protected health information (PHI).

Roles of Targeted Audience and Users

The electronic communication platform allows for multiple users to be logged on at the same time, including EMS, ED staff, radiology staff, stroke team, NI, angiography staff, stroke wards, and administrators, given the nature of required simultaneous input of data in the situation of an acute stroke (**Figure 2**). It provides tiered-level of access to data based on individual staff roles so that patient confidentiality and clinical relevance is maintained throughout the process. It should also allow for revision of incorrect information to maintain accuracy of data that is entered into the application.

The platform is designed with relevant fields of input tailored to individual roles along the care pathway, and each specialty's data logs can be referred to in the future. This facilitates the auditing process, quality assurance, and data collection for research.

Mobile Platform and Web Browsers

Mobile smartphones are now ubiquitous among health professionals and are crucial for effective communication. Key features of smartphones include the touchscreen, push notifications, and security. Touchscreen interfaces are efficient, intuitive, and highly flexible. Push notifications are alerts which trigger even if the phone is not being used actively. These can be audio or tactile and blend into the background use of the phone. A read receipt system is implemented to close the communication loop between team members. Much more information can also be conveyed than in a traditional paging system. Security features in the iOS (Apple Inc, California, U.S) and Android (Google LLC, California, U.S) systems, two of the most common smartphone platforms, also ensure that the information is stored safely and all applications are routinely reviewed by proprietors to ensure they are free of malicious software.

While mobile devices have many advantages, a secure, computer-based intranet system is also a necessity in modern hospitals. This ensures the protection of an individual

TABLE 1 | Potential systemic barriers to timely reperfusion therapy.

Community	EMS	Hospital
BARRIERS TO TIMELY REPERFUSION		
Delayed or mistaken identification of stroke	Delay in arrival or inappropriate triage	**Delay in initial assessment or triage**
Delay in alerting EMS	**Delayed assessment and information gathering**	**Delay in imaging acquisition or review**
	Delayed decision-making	**Delayed decision making**
	Transport to hospital	**Delay in activation of mechanical thrombectomy team**
		Delay in transfer from the emergency department to angiography
		Delay in transfer from an ED to another mechanical thrombectomy-capable hospital

Those in bold may be addressed by an electronic communications application (9).

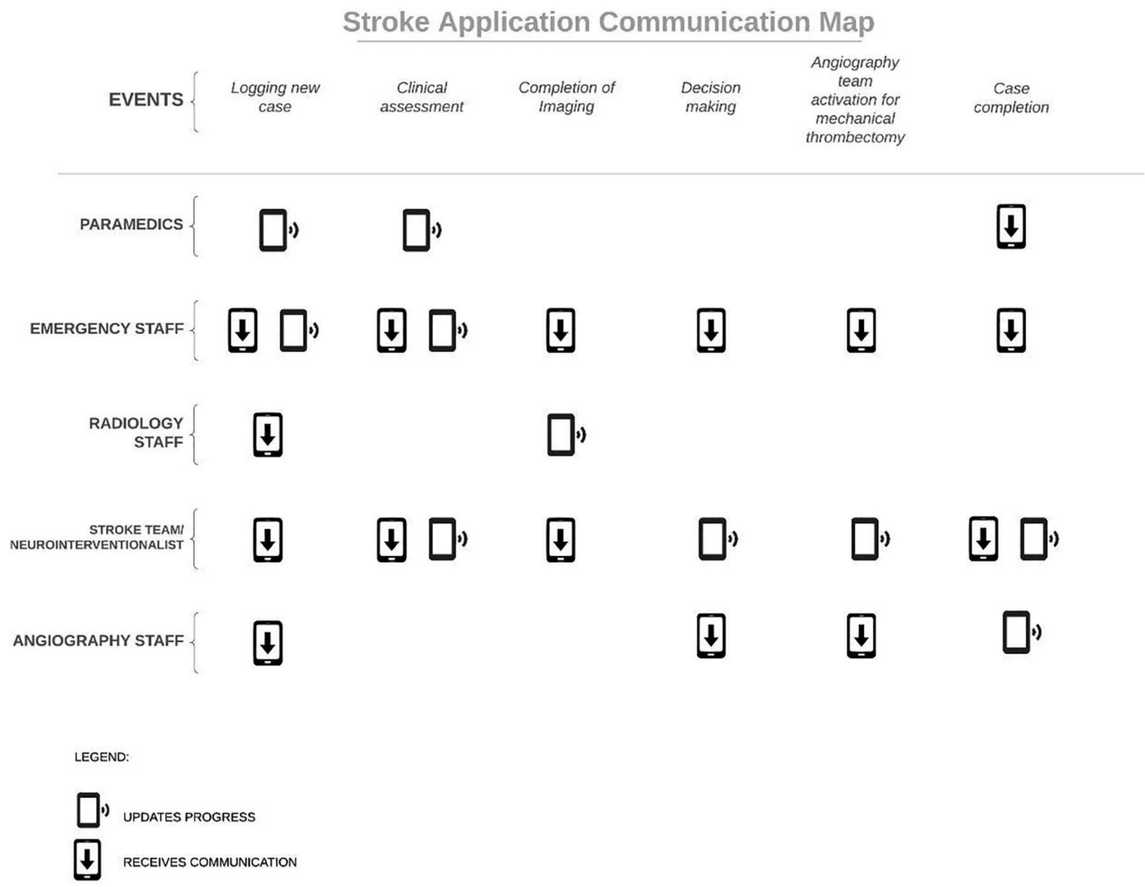

FIGURE 2 | Communication of various events in an acute stroke between different teams with tiered notifications.

health networks PHI through the hospital firewalls and allows for ongoing use and information retrieval even when offline.

User Interface

An ideal user interface (UI) is intuitive and allows tasks to be completed in an efficient and reliable manner. The Code Stroke Alert platform incorporates clarity, legibility, and comprehensibility to allow for a user-friendly, purpose-built application. This is especially important for a healthcare-related application, anticipating a large number and high turnover of users. The application needs to be intuitive so that new users are able to use the platform effectively without extensive training (**Figure 3**).

Tiered Notifications

Tiered notification is a main feature of the electronic communication platform because it allows for users to only be notified with events that are relevant to their clinical specialty and domain of responsibility. The main concern for ongoing and

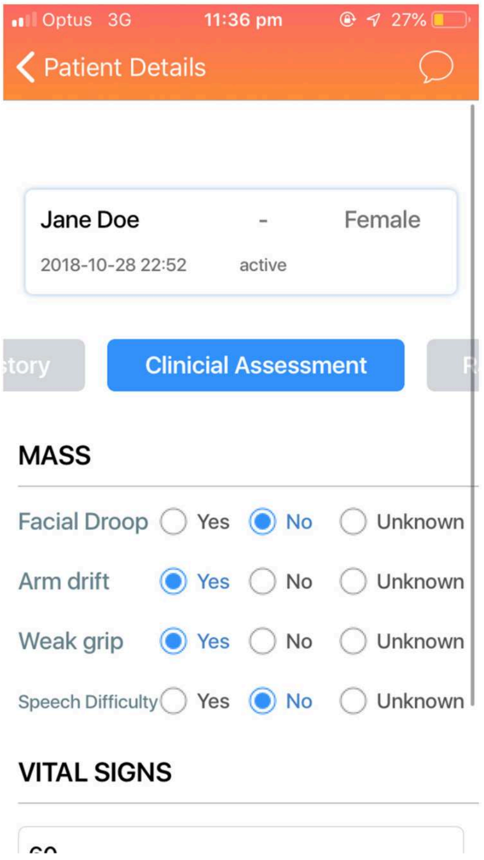

FIGURE 3 | The MASS that has been completed by the paramedics.

continuous notifications in a busy health network with frequent stroke cases is alarm fatigue. Like instant messaging notifications, if there are too many and frequent notifications, users may stop noticing them.

Geotagging and Geolocation

Geotagging is a relatively new technology that allows for geographical location of an electronic device to be identified. Code Stroke Alert uses the Google Location application program interface (API) for real-time location tracking while using the application. As such, it is not required for users to run a separate map application for geotagging. This feature is helpful in acute stroke, tracking the patient's location to provide a relatively accurate estimated time of arrival (ETA) with traffic conditions taken into account, to ensure appropriate resource allocation and prioritization, especially in situations where there are multiple impending acute stroke arrivals. Users will first need to allow location detection while using the application when registering for the first time. The physician's location can be geotagged in a way that ETA of the various treating physicians will be available to users, but not the accurate location for privacy purposes. This ensures that other relevant users are informed with the ETA of on-call specialists and can prepare the patient. This function can also be switched off by individual users if desired.

Security

The most widely used security regulation is the HIPAA, which is a set of rules that dictate the requirements of a healthcare-related application to ensure the three fundamental security goals of confidentiality, integrity, and availability are maintained during transfer of patient information. To help identify possible risks for data breaches or privacy violation, regular audits of the application will be performed. An effective mechanism to communicate errors and bugs in the application between users and developers has been established.

Multi-factor authentication is increasingly used to ensure security of individual accounts. Traditionally, login credentials are made up of a username and a password. However, passwords are becoming easy targets for theft especially when users have weak passwords, the same passwords for multiple applications and have passwords unchanged for long periods of time. Multi-factor authentication in Code Stroke Alert provides an extra layer of security by requesting additional evidence of user credentials.

RESULTS

We have developed Code Stroke Alert, an HIPAA compliant, open-source platform to streamline and synchronize the flow of clinical information, as it is communicated between different members of health care services during the pre-hospital, in-hospital, and inter-hospital care of patients with acute ischaemic stroke.

Roles of Targeted Audience and Users

Code Stroke Alert is intended to cover the entire journey of a stroke patient from the initial contact with a healthcare provider, until return to the ward following treatment completion. We first highlight the professionals involved and how the application is intended to streamline their role in the management of a stroke patient, based on the Australian Health care context.

Paramedics

Paramedics are responsible for identifying and logging most new, suspected stroke cases. Once they have assessed the patient, they are able to log in to Code Stroke Alert and create a new case by inserting basic demographic information, symptoms, and time of onset. There will be other optional fields available including vital signs, weight, or the Melbourne Ambulance Stroke Screen (MASS), next of kin details and a photo of the patient's identification card. This information is broadcast simultaneously to all relevant team members. The paramedics subsequently receive confirmation of receipt, closing the loop of communication. All of the information provided will help facilitate timely assessment and processing upon arrival at the emergency department.

Emergency Department Staff

The ED staff consists of administrative staff, nurses, including those in triage and the main department, and physicians. They are responsible for priority registration of the incoming stroke code, rapid triage, allocation of an appropriate bed, adequate intravenous cannulation, initial blood tests, and facilitation of rapid transfer to the CT scanner. In the event that the patient presents directly to ED rather than via EMS, the ED staff replace the role of the paramedics. The registration details are completed in Code Stroke Alert to ensure nothing is overlooked and completion of these events is updated in the patient file in real-time for all team members, ensuring provision of contemporaneous information and progress.

Radiographers

When the radiographers receive notice of the stroke code they can pre-register the patient with the information provided, allowing them to proceed directly to scanning upon arrival. Once the relevant imaging studies are completed, the radiographers can notify the radiologist and stroke team with a simple check button, as well as inform them of any obvious abnormalities. When imaging is completed, another notification can be sent to all relevant parties to facilitate transfer, either to the angiography lab or back to the ED.

Diagnostic Radiologist

The diagnostic radiologist receives early alert of the estimated time and actual arrival of the patient in ED. This allows them to prioritize review of the images and assess for intracranial LVO, intracranial hemorrhage (ICH), or perfusion abnormality. These findings can be broadcast via Code Stroke Alert to the rest of the team and in particular, to the NI if LVO is suspected.

Stroke Team

The stroke team variably consists of a consultant neurologist, nurse practitioner, and/or junior medical doctors. The stroke team receives early notification of an arriving stroke via Code Stroke Alert. Occasionally, the stroke team will need to log a new case, for acute inpatient stroke events. The application also allows for review of the clinical information gathered by paramedics or emergency staff which can be especially helpful in triaging multiple, simultaneous cases. The stroke team can also easily disseminate the National Institutes of Health Stroke Scale (NIHSS) score and other relevant history or examination findings via Code Stroke Alert. Based on the imaging findings and discussion with the diagnostic radiologist, the stroke team will make a decision on the next step in management which may include mechanical thrombectomy, IV tPA or no intervention. The relevant teams should have been forewarned via Code Stroke Alert, enabling rapid deliberation and transfer from the CT scanner. Finally, the stroke team is informed of the completion and outcome of mechanical thrombectomy and the patient's destination on the ward where they can be reviewed post-procedure.

Neuro-Interventional Team

The neuro-interventional team consists of NI, radiology (angiography) nurses, and radiographers.

NI will be able to follow the progress of a stroke case via Code Stroke Alert, allowing for early independent or collaborative review of the imaging. If mechanical thrombectomy is viable they will be notified early by alerts in the application and can activate the angiography staff (**Figure 4**). Upon completion of the case, relevant information regarding imaging outcomes including reperfusion grading, complications, and post-procedure instructions can be transmitted via Code Stroke Alert.

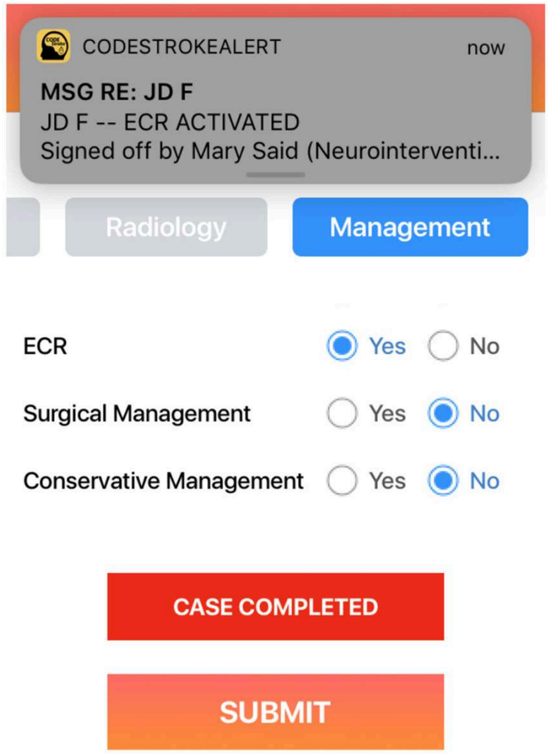

FIGURE 4 | The NI who has been constantly updated with the patient's journey can review the images and activate the mechanical thrombectomy team.

Angiography staff will be pre-notified of a new stroke case and can follow the progress in the application. If the case proceeds to mechanical thrombectomy, the team can be activated via a simple command in Code Stroke Alert. Clinical information can also be reviewed prior to commencing the case and the record kept in the application facilitates handover between nurses and anesthetics team. If the patient is not to proceed to angiography, the staff will also receive a notification to that effect.

Anesthetics Team

The anesthetics team consists of the anesthetist and anesthetic nurse, who attend stroke cases during mechanical thrombectomy for airway and anesthetics support. For each case, a decision is made whether intubation is required for the stroke patient and choice of sedation to administer.

Allocation of the anesthetics team is coordinated by the anesthetist-in-charge and the theater floor coordinator. Involvement throughout the communication process aids with triaging and pre-planning of anesthetic resources.

Stroke Ward

The stroke ward receives early notification when a new case is logged and when the management for the patient has been decided. The acuity of the patient and treatment pathway will have strong bearing on the ultimate destination. Typically, if the patient has a stable airway after extubation, care on a specialty stroke unit will suffice. A patient who cannot be extubated at the completion of mechanical thrombectomy treatment requires admission to ICU. The ease of communication afforded by Code Stroke Alert facilitates these bed management decisions and overall hospital patient flow.

Administrators

The administrative team consists of the Information Technology (IT) staff at individual hospitals to provide support for users of Code Stroke Alert. They are able to access bug reports and customize the application to meet the unique requirements of each hospital. They can also modify plug-ins and add-ons with Picture Archiving and Communication system (PACS) or hospital information system (HIS) integration. Finally, administrators are able to access the database and export data for research and audit purposes.

Mobile Platform and Web Browser

Code Stroke Alert is designed for integrated use between a web browser and mobile application. There are a number of differences between the two systems, primarily in remote access, forced upgrades and bug reports. Firstly, users can only access Code Stroke Alert on a web browser on a computer within the hospital network. Remote access is only allowed on mobile phones. This is necessitated as a matter of security for the web browser which does not have the same in-built security of a phone. The second difference between using Code Stroke Alert on a web browser compared to mobile phone application is in regards to software updates. As it is more common for automatic mobile phone upgrades to be turned off, Code Stroke Alert forces users to upgrade to the latest version of the application on their mobile phones whenever a new version is available. Forced upgrading of Code Stroke Alert with minimal frequency is important to reflect bug fixes and security patches, so that the application is safer for users. Upgrading is not required for Code Stroke Alert on web browsers as the application is automatically updated when the website is refreshed. Finally, when an error occurs with Code Stroke Alert, mobile application users are able to report errors by shaking the device which will automatically forward an error report to the software developers. Feedback on web browsers needs to be manually reported via email to the development team.

Programming Language

Code Stroke Alert uses the programming language Python (Python Software Foundation, Delaware, U.S.) for back-end programming. The back-end is important for data processing and allows information to be requested and sent through to the users. The server is then updated with the latest data that is received through input by users on Code Stroke Alert, allowing all users to have access to updated information about the patient.

Python is a very popular programming language within the medical and scientific community and was selected for its up-to-date and well-maintained libraries and flexible modules, frameworks and packages. This allows for a greater degree of customization to meet the needs of individual health networks.

The database where Code Stroke Alert stores information is written in the programming language MySQL (Oracle Corporation, California, U.S.). MySQL is an open-source Relational Database Management System (RDBMS) that uses Structured Query Language (SQL). SQL is used for adding, accessing, and managing content in a database, and is noted for its quick processing, flexibility, reliability, and ease of use.

The front-end is the part of the application that users interact with directly. The front-end of the iOS version of Code Stroke Alert is written in the programming language Swift (Apple Inc., California, U.S.), which is a relatively new open-source programming language developed and supported by Apple. The front-end of the Android version of Code Stroke Alert is written in the programming language Java (Oracle Corporation, California, U.S.), similar to the language that was used to write Android itself. It is a very popular and reliable language for writing Android applications and has been established for more than 20 years.

User Interface

After initial discussion regarding the functionality requirements and information architecture, the initial wireframes were developed on *Balsamiq* (Balsamiq studios, California, U.S). Feedback from health professionals was then sought to review button choices, sizes, information flow, wording, input controls, and other elements of the user interface.

Free text entry boxes are selected for data fields with unlimited possible input such as patient name, address, phone number, clinical history, past medical history, and medication lists so that data can be entered freely on the platform. Data with limited possible input such as gender are listed as options for easy selection. Similarly, the options for each component of clinical scores are also listed as options so that calculation of the score is possible. Fields with numerical data such as time last seen well, date of birth, blood pressure, heart rate, weight, and oxygen saturation are entered as a scrollable list of numbers.

To expedite data entry, commonly prescribed anticoagulants are listed together with the medication text box that can be ticked if the patient is currently on a particular anticoagulant given its clinical relevance. Relevant past medical history including hypertension, diabetes, previous strokes and ischaemic heart disease are also listed together with the past medical history free-text box.

The final wireframes were developed after an iterative back-and-forth process. A straightforward design and a minimal and concise approach were adopted for the user interface of Code Stroke Alert to optimize usability of the application.

Content

Even with an efficient touchscreen input, reliable backend programming and an intuitive UI, every extra piece of information which requires input into Code Stroke Alert is time spent away from assessing and managing the patient. Content selection has been balanced to ensure adequate vital information is entered, whilst minimizing downtime and user fatigue.

For emergency services, some essential information is required, including patient identification, height and weight, destination hospital, and basic presentation including vital signs and last time the patient was seen well. Some aspects of the patient ID can be automatically derived from the mobile phone camera and an ID card and destination hospital automatically defaults to the geographically closest hospital. The remainder of the EMS interface involves clinical history and assessment. Here, relevant and common medical issues such as ischaemic heart disease, diabetes, previous strokes and any anticoagulant use can be easily selected using yes/no checkboxes, and there is additional, non-mandatory, free text input area for other information the paramedics deem to be important.

The MASS, a screening tool currently used by Ambulance Victoria, is included in Code Stroke Alert to aid with diagnosis of stroke. While it is useful, it is not a mandatory input, as this assessment can be complex, and the result will not alter the need for imaging. A prompt is also included to insert an 18G intravenous cannula to facilitate contrast power injection for CT angiographic stroke imaging upon arrival at hospital, or subsequent thrombolysis. This is an important step which can delay imaging, thus justifying its specific inclusion as a prompt. A summary page is also included, providing a quick review of the information provided, which can be performed in transit.

For hospital staff Code Stroke Alert is divided into a page detailing all incoming, active, and completed stroke codes which lead to the individual patient pages containing their details. Often multiple stroke codes occur concurrently and several can occur in a day. It was deemed necessary to have a quick way of listing all current stroke patients, differentiating between them, and tracking their general progress. The information collected within Code Stroke Alert is derived from that which is deemed necessary by physicians and non-clinical staff to provide management in hospital. Within the individual patient pages, current location and primary survey data are followed by the EMS, and finally sections for in-hospital assessment and management. This last section includes NIHSS, modified Rankin score (mRS) and tabs to facilitate imaging and communicate treatment decisions. The NIHSS allows for baseline comparison pre- and post-treatment. The mRS guides the ceiling of treatment that would be offered to patients. The imaging information is especially important when multiple CT scanners are in use. Completion of the scan and early diagnostic results can be quickly communicated with checkboxes in the individual patient page, as can the decision for thrombolysis, mechanical thrombectomy, or conservative management.

Tiered Notifications

The notifications broadcasted by Code Stroke Alert are filtered and tiered to prevent alarm fatigue. The notifications are tailored to individual roles so that users only receive relevant notifications. For example, when the CT is marked as completed by the radiographer, the notification is sent to the stroke team, the NI and the diagnostic radiologist but not to ED staff, the angiography team or the stroke ward as these staff are not required to review the images immediately to devise a management plan. By filtering the notifications and only activating physicians at appropriate timepoints, alarm fatigue can be reduced and user satisfaction can be maintained. Users are also able to unsubscribe to notifications for a particular case if they do not wish to receive alerts about a particular patient but still want to be informed of the outcome of the case. For example, this would be relevant for a Stroke consultant who may not be on-call that day but will be looking after the stroke patients the following day. Ultimately, the system may be adapted to the needs of each health network, team, and individual.

Other Features

Code Stroke Alert has been designed to provide assistance to all parties involved in acute stroke care through a number of carefully selected features.

Geolocation and geotagging allows for the automatic recommendation of the nearest and most appropriate hospital and for real-time location to be broadcast to all team members. The estimated time of arrival of both the patient and NI, if they are off-site, can also be automatically broadcast, although the exact location of the NI is withheld for privacy.

As discussed, multiple clinical score calculators such as the NIHSS, MASS and mRS are integrated into Code Stroke Alert. They provide useful predicative information and have been designed within the application to allow for ease of tabulation. Automatic clinical prompts are also designed to popup based on input information such as warnings against thrombolysis if anticoagulation is noted. While they are useful, the risk of alarm fatigue and excessive prompting is recognized and Code Stroke Alert is designed to be modular to allow for individual health networks and teams to tailor the system to their preference.

In addition, Code Stroke Alert provides a secure communication platform between all users. The platform allows for instant messaging with read receipts to prevent breakdown of communication and avoid duplication. It also allows for photos and videos to be shared within the chat group if required. This feature can be particularly helpful for recording the patient's neurological deficit or recording the acquired CT images if some physicians are off-site and do not have direct access to Radiology or are not able to examine the patient themselves.

In the event that the users of Code Stroke Alert do not have their mobile phones with them, there is an option to integrate its notifications with the conventional paging system. In such cases, the tiered notification system will be applied to the paging system.

Code Stroke Alert is also open source making the application easily customizable to adapt to the individual needs of the health network or team. Synchronization with PACS and HIS systems is also possible providing automatic access to radiology and the patient's medical record via Code Stroke Alert.

Furthermore, all data entered into Code Stroke Alert are timestamped and securely stored. The collected data is useful for quality improvement and research purposes. The users of Code Stroke Alert can share this information easily and securely with other hospitals if they choose to provide efficient handover to physicians from other health networks, and to assist in collaboration and improving overall patient care.

Finally, to assist with the debugging process in the trial phase of Code Stroke Alert, users are able to log a bug report by just shaking their mobile phones which will create a free text pop-up box which will feed back directly to the development team. The bug report captures the actual moment and page that users are experiencing problems. It is designed to be as simple as possible to maximize the chance busy healthcare professionals will report issues.

Security and Legal Compliance

Code Stroke Alert is fully compliant with the HIPAA. The platform uses secure sockets layer (SSL)/transport layer security (TLS) encryption and decryption for all data transfer requests, which is a security protocol to ensure data encryption, integrity and authentication. This is to prevent sensitive PHI from being leaked to unauthorized parties.

All users will have a login page for security reasons. To strike a balance between security and user fatigue, a single login is required every 24 h. Code Stroke Alert uses multi-factor authentication to increase the security and protect users of the platform.

Code Stroke Alert has a decentralized database and has pieces of information stored in different locations which are all connected to each other. With a decentralized network and data distributed amongst multiple nodes, all data is backed up on multiple nodes and constantly protected if any data is maliciously altered. This eliminates vulnerability to hacking as all of the nodes that hold the data would have to be attacked at the same time to destroy data on the decentralized network. It also prevents accidental change of data. Furthermore, in the event of compromise of any individual node, the remaining nodes can retain function with data transfers as the damaged node is being replaced or repaired.

Lastly, Code Stroke Alert is made secure by storing the database within the server of the health network. It is kept as secure as possible by the existing firewall and demilitarized zone of the hospital's network.

DISCUSSION

Code Stroke Alert is a digital platform designed to streamline the communication process in the acute management of stroke. It is a user-friendly, purpose-built application that offers convenient means of data entry and sharing.

There is an increasing use of mobile devices and applications by health care providers to assist with many important tasks, including information and time management, health record maintenance and access, communications, information gathering, patient management and monitoring, clinical decision making, and medical education and training (10). In a survey of healthcare providers and medical students, more than 80% of respondents described using e-mail, telephone, or text messages to communicate with colleagues about patient care, as it is described to be a more efficient way of communication than meeting in-person or having a phone conversation (11).

Usage of mobile applications have provided many benefits to health care providers, such as convenience, increased efficiency, and enhanced productivity. Code Stroke Alert is convenient for users as it is able to be accessed through hospital computers or personal devices. It allows users to utilize the application while they are not on hospital grounds. Code Stroke Alert also increases efficiency by allowing clinicians to triage and plan their time around the arrival of these stroke cases and to allocate resources effectively based on clinical urgency.

TABLE 2 | Features of Code Stroke Alert, Join application, and Stop Stroke.

Features	Code Stroke Alert	Join application	Stop Stroke
Pre-hospital notifications	✓	✓	✓
Comprehensive intra-hospital notifications	✓	✓	✓
Inter-hospital notifications	✓	✓	✓
Open source	✓	✗	✗
Customisable	✓	✗	✗
Data collection	✓	✓	✓
Geolocation	✓	✓	✓
Secure messaging	✓	✓	✓
Full iOS, android and web browser functionality	✓	✗	✗

The use of mobile applications during delivery of acute stroke care is well-known in stroke literature. The Join application (Allm, Inc, Tokyo, Japan) and Stop Stroke (Pulsara, Montana, U.S.) are two of the several existing communication applications to enhance the coordination and communication in delivery of acute stroke management (12, 13). **Table 2** outlines the features that are offered by Code Stroke Alert, Join application, and Stop Stroke.

To our knowledge, Code Stroke Alert is the first stroke communication application that allows individual health networks to customize the application to their needs through an open source feature.

It is also the first stroke communication application that can be used on web browsers as there are staff involved in the stroke communication pathway who are normally stationed at a particular computer throughout their shift. Allowing Code Stroke Alert to be used on web browsers prevents these staff from having to swap between their computers for work purposes and mobile phones to check Code Stroke Alert notifications.

Current Progress and Utility

Code Stroke Alert is currently approved for trial at two Comprehensive Stroke Centers in Australia. This trial follows approval from multiple services in these centers, including Emergency, Radiology, Stroke, NI, and Information Technology Departments.

The effectiveness of the platform will be evaluated using a pre-post historical design to study the impact of Code Stroke Alert implementation upon time to reperfusion therapy. In these facilities, detailed treatment and outcome records for comparison. Further improvements will be made to the platform based on user feedback prior to trialing Code Stroke Alert on a larger scale using a stepped wedge cluster randomized trials.

The initial trial setting will also be used to actively monitor and remove glitches and bugs and to implement further user-friendly features, with the goal of seamlessly integrating the application with day to day stroke unit work flow, tracking a patient through their entire hospital journey. There is ongoing designer and developer support for integration with the individual hospital PACS and HIS, as well as relevant EMS applications and programs, with the intension of optimizing the usability of the platform.

The final goal of the trial process is to further develop the application into a stand-alone application that is free to download and implement easily in stroke units around the world without the need for developer installation, extensive support, and troubleshooting.

Research Potential

Data entered into Code Stroke Alert are saved into a secure, de-identified database on the hospital's network. This rich database with archived data from the hospital's stroke cases can be audited and analyzed in the future for quality improvement, for planning appropriate service funding, resource allocation and service development, expansion of facilities and for research purposes.

CONCLUSION

Code Stroke Alert is a new, user-friendly, purpose-built application to streamline hyperacute stroke management. It incorporates high-level mobile-oriented features like geolocation and push notifications to improve multidisciplinary communication. After testing is complete, the back-end coding for Code Stroke Alert will be made freely available to researchers globally, with potential for customization to meet the needs of individual health networks and widen the scope to other time-critical diseases.

DATA AVAILABILITY

All datasets are included in the manuscript.

AUTHOR CONTRIBUTIONS

HS, MBu, BC, JM, RC, VT, MBr, BT, and HA contributed conception and design of the application. MBu, MP, DS, JW, OB, and JT developed the application. HS and KZ wrote the first draft of the manuscript. HS, KZ, GY, CB, and HK wrote sections of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Googling Service Boundaries for Endovascular Clot Retrieval (ECR) Hub Hospitals in Metropolitan Sydney

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Background and Purpose: Endovascular clot retrieval (ECR) has revolutionized acute stroke therapy but is expensive to run and staff with accredited interventional neuroradiologists 24/7; consequently, it is only feasible for each metropolitan city to have a minimum number of hubs that is adequate to service the population. This method is applied to search the minimum number of hospitals to be designated as ECR hubs in Sydney as well as the population at risk of stroke reachable within 30 min.

Methods: Traveling time from the centroids of each suburbs to five ECR capable hubs [Royal Prince Alfred/RPA, Prince of Wales/POW, Royal North Shore/RNS, Liverpool/LH and Westmead/WH]. This step was performed using *ggmap* package in R to interface with Google Map application program interface (API). Next, we calculate the percentage of suburbs within each catchment in which traveling time to the ECR hub is <30 min. This step was performed for all possible combination of ECR hubs. The maps are available at https://gntem3.shinyapps.io/ambsydney/. The population at risk of stroke was estimated using stroke incident studies in Melbourne and Adelaide.

Results: The best 3-hospital combinations are LPH/WH/RNS (82.3, 45.7, and 79.7% of suburbs reachable within 30 min or 187 of 226 suburbs) follow by RPA/LPH/RNS (100.0, 80.9, and 73.1% of suburbs) and LPH/POW/RNS (83.3, 90.7, and 76.6% of suburbs). The best 4-hospital model is LPH/WH/POW/RNS (84.2%, 91.1%, 90.7%, 77.8%). In the 5-hospital model, ECR is available for 191 suburbs within 30 min: LPH (83%), RPA (100%), WH (90.2%), RNS (72.7%), POW (88.9%). Based on 3-hospital model and 15% of patient eligible for ECR, the expected number of cases to be handled by each hospital is 465. This number drops down to 374 if a 4-hospital model is preferred.

Conclusions: The simulation studies supported a minimum of 4 ECR hubs servicing Sydney. This model provides data on number of suburbs and population at risk of stroke that can reach these hubs within 30 min.

Keywords: clot retrieval, stroke, geospatial, Google Map API, optimization, simulation

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INTRODUCTION

Recent advances in stroke therapy has generated debate on translating clinical trial findings to service the entire population (1–6). This is an issue which come to the attention of mainstream media from time to time when the ability of the team to provide 24/7 did not meet public expectation (7). This case in 2016 illustrated that even 1 year after publications the ECR trials, the ability to translate findings into clinical practice can remain elusive. It is possible that the enormous logistic required to bring together a highly skilled teams comprising of interventional neuroradiologists (INR), stroke (vascular) neurologists, support staff (anesthetists, neurosurgeons, trainee doctors, radiographers, and nurses), and dedicated angiography suites and bed availability financially supported by the government (8).

In Australia, the state of Victoria and South Australia have set up a statewide service protocol (9) for ECR immediately after the publication of the ECR trials (1–6). This idea is similar to the concept of comprehensive stroke center (CSC) but with a difference that the CSC provide care for the catchment and also outlying rural areas (10). In this framework, two hospitals were designated as ECR hubs from a pool of 4 ECR capable hospitals. These ECR hubs are required to provide a 24 h service not just for patients in their immediate local catchment but also for all residents of the states. Using a data driven approach, we showed that it was possible to service most of Melbourne within 30 min with 2 ECR hubs (11). In this paper, an idealized time of 30 min is used based on the modeling in the redesign of stroke service in London (12). A similar process has been developed in South Australia, with one hospital providing ECR service from a pool of 3 ECR capable hospitals. Such a service is in development in Sydney, New South Wales but as yet an official policy statement has not been released (13). Using method for mapping catchment areas in Melbourne and Adelaide (11), we apply similar approach to search the minimum number of hospitals to be designated as ECR hubs in Sydney. Further, we estimate the ECR case load for each combination of hospital to help determine the minimum number of hospitals required as ECR hubs.

METHODS

Setting

Sydney is the capital city of the state of New South Wales, Australia with a population density of approximately 407 person per km^2 in greater Sydney (https://www.abs.gov.au/). Excluding the surrounding parks, the population density is 1237 person per km^2. The postcodes for metropolitan Sydney are in the range 2000–2234, 2555–2567, 2761–2768. The 2016 census data from each postal area in New South Wales can be obtained from https://datapacks.censusdata.abs.gov.au/datapacks/. The number of strokes was estimated using the census data for each age band and the stroke incidence study in Melbourne and Adelaide (14, 15). This study involves simulations (no patient data are used) and as such received a waiver from the Monash Health Human Research Ethics Committee.

ECR Capable Hospitals in SYDNEY

At present there is no official statewide protocol for ECR in Sydney (https://www.aci.health.nsw.gov.au/networks/stroke). There are five hospitals (Royal Prince Alfred/RPA, Prince of Wales/POW, Royal North Shore/RNS, Liverpool/LH and Westmead/WH) capable of acting as ECR hubs. The John Hunter Hospital provides ECR service in Newcastle, 162 km to the North of Sydney. This hospital (postcode 2305) is not considered as part of Sydney catchment. Each of the ECR capable hospitals were considered as a potential ECR hub for the simulation. Membership of a hub was determined using logical comparison of traveling time from each address to the different ECR hospitals. Within each catchment, we calculate the percentage of suburbs in which traveling time to the ECR hub is <30 min. This step was performed for all possible combinations of ECR hubs. The locations of the ECR capable hospitals relative to these arterial roads can be seen in **Figures 1**, **2**. The best combination of ECR hubs were defined according to travel time.

Google Map API

We used *ggmap* package R (R Project for Statistical Computing, version 3.4.4) to query Google Map application program interface (API) (https://developers.google.com/maps/) (16). The transport times to each hospital from each suburb centroid were computed for morning peak hour traffic.

Shiny and *Leaflet* Display

Results of analyses were displayed as interactive web-based maps using R package leaflet and tiles from OpenStreetMap (©OpenStreetMap contributors. For copyright see www.openstreetmap.org/copyright) (17). These maps were uploaded using *Shiny* onto the web (RStudio Inc) available at https://gntem3.shinyapps.io/ambsydney/.

RESULTS

The results are available in **Table 1** and on the web. The best 3-hospital combinations are LPH/WH/RNS (82.3, 45.7, and 79.7% of suburbs reachable within 30 min or 187 of 226 suburbs) follow by RPA/LPH/RNS (100.0, 80.9, and 73.1% of suburbs reachable within 30 min, 184 of 226 suburbs) and LPH/POW/RNS (83.3, 90.7, and 76.6% of suburbs reachable within 30 min, 184 of 226 suburbs).

The best 4-hospital model is LPH/WH/POW/RNS (84.2%, 91.1%, 90.7%, 77.8% reachable within 30 min or 200 of 226 suburbs). This model provides better coverage than the next best 4-hospital model (RPA/LPH/WH/RNS) by 11 suburbs and the next best 3-hospital model (LPH/WH/RNS) by 13 suburbs.

In the 5-hospital model, ECR is available for 191 suburbs within 30 min: LPH (83%), RPA (100%), WH (90.2%), RNS (72.7%), POW (88.9%). The 5-hospital model is not superior to the 4-hospital model because RPA is situated in the center of LPH/WH/POW/RNS.

The estimated number of patients that can be treated with each model for each hospital are provided in **Table 2**. The maximum estimated population reachable within 30 min is observed in 3-hospital model 8 (LPH/WH/POW—9292 cases),

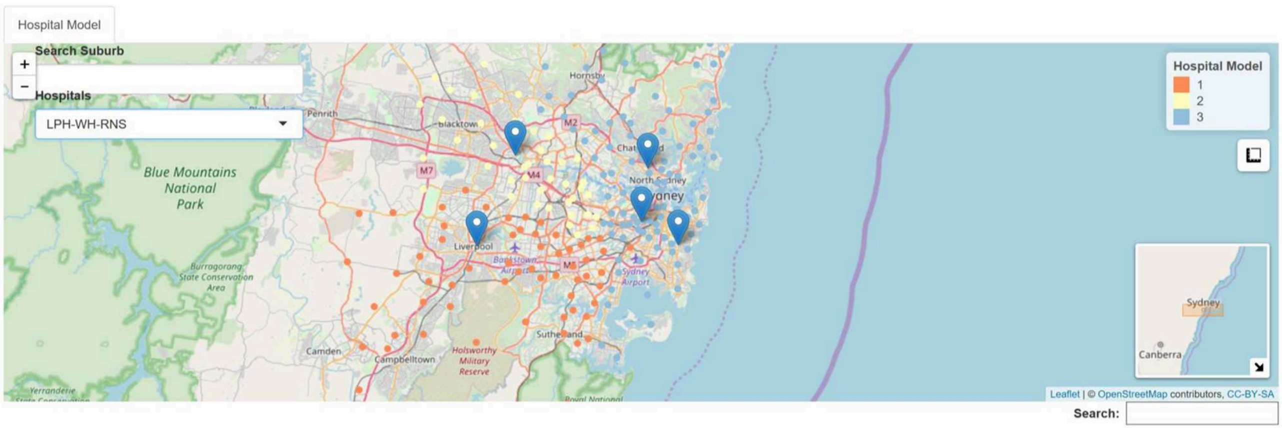

FIGURE 1 | Example of 3 hospital model. RNS, Royal North Shore Hospital, light blue; LPH, Liverpool Hospital, orange; WH, Westmead Hospital, light yellow.

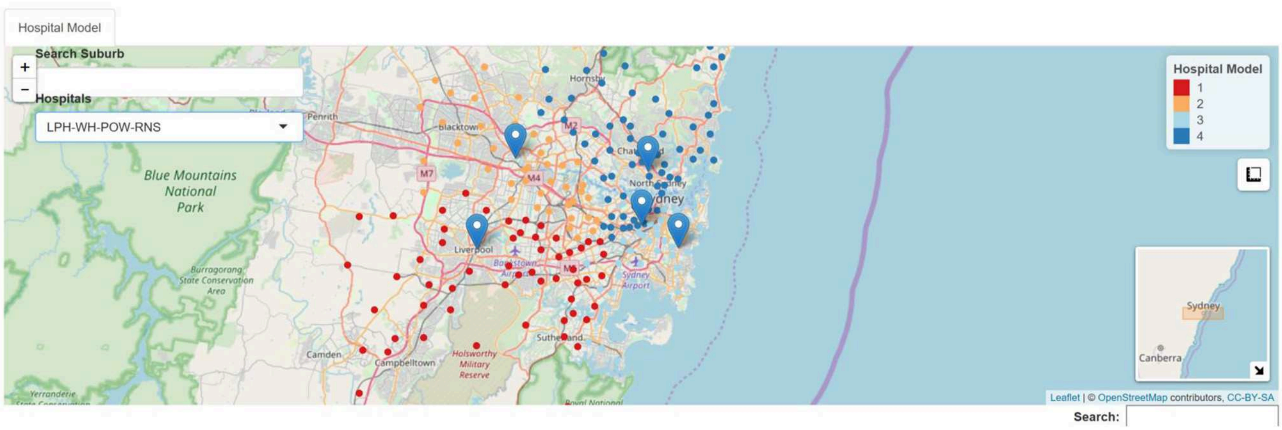

FIGURE 2 | Example of 4 hospital model. RNS, Royal North Shore Hospital, blue; LPH, Liverpool Hospital, red; WH, Westmead Hospital, orange, POW, Prince of Wales Hospital, light blue.

follow by model 6 (LPH/POW/RNS—8982 cases) and by model 1 (RPA/LPH/WH—8559 cases). The maximum estimated population reachable within 30 min is observed in 4-hospital model 5 (LPH/WH/POW/RNS—9991 cases), follow by model 2 (RPA/LPH/WH/RNS—9363 cases).

The number are lower if based on the Adelaide stroke incident study (15) and higher if based on Melbourne stroke incident study (see **Table 1**) (14). These hospitals serviced the largest population at risk of stroke. Based on 3-hospital model and 15% of patient eligible for ECR, the expected number of cases to be handled by each hospital is 465. This number drops down to 374 if a 4-hospital model is preferred.

DISCUSSION

In this study, we have used data driven method to map service boundaries for ECR hubs based on Google Map API estimate of travel time to the hub in Sydney. We estimated that the minimum number of hubs to service Sydney is 4 based on the number of suburbs and population at risk. Further below we will discuss if it is possible to have 4 ECR hubs given availability of INR in Sydney, Australia. Our extension of the methodology to estimation of population at risk will be useful for planning capacity of health services.

In our initial publication on the map of ECR hub catchment for Melbourne, we were challenged by the reviewers to demonstrate that the method could be applied elsewhere (11). We subsequently added the catchment area of ECR hubs for Adelaide, Australia, and now Sydney, Australia (11). Other investigators have described the use of Google Map API for modeling stroke services in North America (18). As such, we postulate that the method can be applied to any international locations serviced by Google Map API and for any time-dependent conditions such as acute coronary syndrome (19). There are several countries, such as Republic of Korea (South Korea) and People's Republic of China, where Google Map API may not be the optimal tool; Google Map API is available for use in Republic of China (Taiwan).

TABLE 1 | Traveling time and coverage area for different combinations of ECR hub models in metropolitan Sydney.

	Percentage of suburbs within 30 min of RPA	RPA suburbs	Percentage of suburbs within 30 min of LPH	LPH suburbs	Percentage of suburbs within 30 min of WH	WH suburbs	Percentage of suburbs within 30 min of POW	POW suburbs	Percentage of suburbs within 30 min of RNS	RNS suburbs	Total number of suburbs serviced within 30 min	Total number of patients serviced within 30 min*	Total number of patients serviced within 30 min#
3 hospitals-1	76.1	109	77.6	58	76.3	59					173	8559	4997
3 hospitals-2	57.8	109	71.1	76			87.8	41			153	7118	4156
3 hospitals-3	100	50	80.9	68					73.1	108	184	8979	5227
3 hospitals-4	68	75			66.3	92	64.4	59			150	7390	4313
3 hospitals-5	75.9	54					45.3	75	63.9	97	137	6322	3678
3 hospitals-6			83.3	72			90.7	43	76.6	111	184	8982	5228
3 hospitals-7			84.2	57	39.1	69	24	100			174	8624	5034
3 hospitals-8			82.3	62	45.7	46			79.7	118	187*	9292	5412
3 hospitals-9					71.2	80	33.8	65	77.8	81	164	8092	4713
4 hospitals-1	67.6	74	83	53	76.3	59	90	40			175	8641	5044
4 hospitals-2	100	42	81.8	55	90.2	41			73.9	88	189	9363	5456
4 hospitals-3	100	38	81.8	66			88.9	36	72.1	86	186	9061	5274
4 hospitals-4	100	31			71.8	74	61.1	55	72.7	66	166	8193	4772
4 hospitals-5			84.2	57	91.1	45	90.7	43	77.8	81	200*	9991	5815
5 hospitals-1	100	30	83	53	90.2	41	88.9	36	72.7	66	191	7023	4106

Melbourne stroke incident study; #Adelaide stroke incident study.

TABLE 2 | Projected number of patients with stroke serviced by different combinations of ECR hubs.

	Stroke number for RPA* using Melbourne incident data	Stroke number for RPA# using Adelaide incident data	Percentage of suburbs within 30 min of LPH	LPH suburbs	Percentage of suburbs within 30 min of WH	WH suburbs	Percentage of suburbs within 30 min of POW	POW suburbs	Percentage of suburbs within 30 min of RNS	RNS suburbs	Total number of suburbs serviced within 30 min	Total number of patients serviced within 30 min*	Total number of patients serviced within 30 min#
3 hospitals-1	3439	2013	2559	1487	2561	1498	0	0	0	0	173	8559	4997
3 hospitals-2	2425	1415	3105	1808	0	0	1588	933	0	0	153	7118	4156
3 hospitals-3	1759	1043	3148	1833	0	0	0	0	4073	2352	184	8979	5227
3 hospitals-4	2089	1216	0	0	3581	2088	1721	1010	0	0	150	7390	4313
3 hospitals-5	1452	855	0	0	0	0	1578	921	3293	1902	137	6322	3678
3 hospitals-6	0	0	3364	1957	0	0	1627	955	3991	2316	184	8982	5228
3 hospitals-7	0	0	2733	1587	3035	1769	2856	1678	0	0	174	8624	5034
3 hospitals-8	0	0	2837	1647	2270	1332	0	0	4185	2433	187	9292	5412
3 hospitals-9	0	0	0	0	3254	1900	1987	1161	2851	1652	164	8092	4713
4 hospitals-1	1976	1151	2516	1462	2561	1498	1588	933	0	0	175	8641	5044
4 hospitals-2	1544	914	2559	1487	2058	1208	0	0	3202	1847	189	9363	5456
4 hospitals-3	1218	720	3105	1808	0	0	1446	844	3293	1902	186	9061	5274
4 hospitals-4	1116	656	0	0	3077	1798	1578	921	2422	1398	166	8193	4772
4 hospitals-5	0	0	3279	1899	2234	1310	1627	955	2851	1652	200	9991	5815
5 hospitals-1	1003	591	2516	1462	2058	1208	1446	844	2422	1398	191	9445	5503

Melbourne stroke incident study; #Adelaide stroke incident study. The shaded rows represent the combinations with the best coverage.

The use of geographical information systems for health service design is evolving since 2017 with several publications in the journal *Stroke* and *Jama Neurology* (11, 18, 20–22). In this study, we have accessed Google Map API for traffic data due to our familiarity with this platform (11). There are other platforms such as Bing Map API (tarifX and tarifX.geo packages in R), Yahoo (https://github.com/trestletech/rydn) and Baidu Map (https://github.com/badbye/baidumap). Outside of the R environment, there is package in Python for performing geospatial analysis (23) and investigators have also used Matlab (MathWorks[@]) for accessing Google Map API (18). Google Map API has a constraint in that it allows only 2500 queries per day; it charges for additional queries.

The data driven method described here show that selection of ECR hubs for other cities cannot be empirically inferred directly from the Melbourne or Adelaide models. This is likely the case since each city has their individual geography, arterial roads, and locations of ECR capable hospitals. Using the idealistic notion of a maximum 30 min traveling time to the ECR hospital, we can assess the ECR hub location which best suits this requirement. In Sydney, it would appear that the optimal models for 3-hospital and 4-hospital models are combinations of LPH/WH/RNS and LPH/WH/POW/RNS. The suburbs serviced by these hospitals have the largest population at risk of stroke. It is likely that the geography of Sydney makes it difficult to service the population with a small number of ECR hubs such as the case in Melbourne. By comparison, >85% of patients can arrive within 30 min with just 2 ECR hub model in Melbourne (11).

The issue of transport to the most appropriate hospital has been the focus of recent research regarding "drip and ship vs. direct to comprehensive stroke center" (20, 24). These strategies were not evaluated here as that is not the intention of this study. A question arises as to the compatibility of the approach based on 30 min trip to ECR hub and "drip and ship" model of care. Our model provides a mean to address this question directly by showing that a large part of Sydney can be reached within 30 min and thus a direct trip to "mothership" ECR hub is possible. These estimates of the population at risk should not be seen as an endorsement of the strategies of sending all patients to ECR hubs. Rather the estimates are provided as a mean to evaluate the capacity of the system to handle the ECR case load. The ability to handle all caseload is part of the equation in the approach to "drip and ship" vs. direct to "mothership" hub conundrum. There has been an increase number of ECR cases since 2015 (25). However, it has been estimated that approximately 84 to 90% cases do not go on to ECR. In this situation the medical stroke code team can be overwhelmed unless some strategies are put in place to limit the transfer of cases to ECR hub (26). A similar strategy that takes into account the population serviced is used in the evaluation of stroke service in England (27). Even with 4-hospital model the average annual ECR case load is 374. This number is a significant challenge to individual ECR hub and a centralized flexible model is required to return patients to a non-ECR hospital nearest to their residential addresses after acute clot retrieval (12). At present such a flexible model had been described with the London reconfiguration but the durability of the repatriation model is not known. A model for repatriation does not yet exist for ECR in Australia. The Victorian statewide protocol emphasizes repatriation of patients back to referring hospital after ECR. However, it does not provide a mean to enforce the referring hospital to accept the patient once repatriation at present (28). Stroke experts will need to actively engage with local government, chief executives of all hospitals, including ambulance services to design these aspects of statewide ECR services.

In discussion on ambulance transport, one often hypothesizes that ambulances arrive faster at destination when using lights and sirens compares to estimations of travel time by Google Map API. We had compared the travel time between observed (ambulance) and simulated travel time by Google Map API and found minimal difference (approximately 3.5 ± 2.5 min) (11). In Australia, ambulance officers are required to obey traffic light and signs, and required to stop at traffic light, check road condition before crossing road intersections. Google Map API provides direction in accordance with traffic regulations (no traveling in the opposite lane). In some cases, estimation of travel time was much faster by Google Map API. It is possible that when Google Map API provides estimate of best-case scenario, it simulates traffic condition in which all traffic lights are green. This effect may be akin to the emergency vehicle prioritization (EVP) protocol. To our knowledge the EVP system is being trial in Queensland but has not been implemented in Adelaide, Melbourne nor Sydney (29).

Our study has several limitations. The simulations were made under certain assumptions about the interventional neuroradiologists (INR) workforce. In the development of the Victorian ECR model, each site was required to have at least 3 accredited INR (28). The register of accredited INR in the State of New South Wales is available at this web address (http://www.ccinr.org.au/register accessed 23/3/19). With 13 available INR, the number of ECR hubs that can be served would be 4. Taking into account the ECR hub in John Hunter Hospital, there would be just sufficient INR to staff 3 ECR hubs in Sydney. Our proposed model requires that the interventional neuroradiologists are not simultaneously on-call at two ECR hub and that each hub has two angiograph suites. The issue of INR rostering is not a just a theoretical concern with a recent coronial inquest over availability of INR in Adelaide, Australia (30). In the event of such staffing shortage or angiographic suite being used for another reason, the model does not hold true as there is a time cost of transporting the patient and additional cost of transporting the interventional neuroradiologist. In an earlier study of cardiac revascularization service, we had shown the impact staff residential location on providing timely service (19). In that study only 45% of inner Melbourne and 56% of outer Melbourne staff could reach hospital within 30 min. Such considerations were not performed here as it would require access to personal data. Our emphasis on 30 min to hospital can be interpreted as too stringent for other countries or a need for centralization of service. Investigators reported that access to access to intravenous-capable hospitals within 60 min was available to 81% of US population and 56% had access to endovascular-capable hospitals (31). In this analysis, we have not considered ECR experiences, interventional neuroradiologists or infrastructure at a potential hub. Of the 5 potential hubs in Sydney, only RNS and WH had participated in the recent ECR trial (5, 32). While services within each hub can be re-organized with increased funding, it is possible that a bottle neck in the consideration of a site for ECR hub is the availability of interventional neuroradiologists.

Our use of ggmap package and which relies on Google Map API has several drawbacks. Principally, Google Map cannot be used to predict future traveling time. Future scenarios can be performed using purpose built strategic model for each state of Australia (33). Further, the *ggmap* package requires modification to perform trip estimation at different time of day. Some of the newer packages in R such as *googleway* permits specification of time of travel (34). In this study we were reassured in that the results from *ggmap* had differed from real ambulance trips by 3 to 5 min in an earlier study (11).

Another limitation of our approach is the reliance on population based studies in other cities within Australia to estimate the number of stroke patients (14, 15). These studies showed a decline in the number of stroke cases over time and it is not certain if our projections do not overestimate the number of stroke cases and which can impact on configuration of ECR hubs. One approach would be to use a current estimate of the number of stroke cases in Sydney. This data is not available at the time of this analysis.

In summary, we estimated the minimum number of ECR hubs to service Sydney and the optimal combination of sites. The choice of sites and their combinations depends on the government agencies and policy makers.

DISCLOSURE

TP is on the Advisory Board of Genzyme on Fabry Disease and has received payment for lectures including service on speakers' bureaus for Bayer, Boehringer Ingelheim, Pfizer and Genzyme.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

TP: design, analysis, and writing manuscript. RB, VS, and HM: writing manuscript.

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An Introduction to Software Tools, Data, and Services for Geospatial Analysis of Stroke Services

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Background: There is interest in the use geospatial data for development of acute stroke services given the importance of timely access to acute reperfusion therapy. This paper aims to introduce clinicians and citizen scientists to the possibilities offered by open source softwares (R and Python) for analyzing geospatial data. It is hoped that this introduction will stimulate interest in the field as well as generate ideas for improving stroke services.

Method: Instructions on installation of libraries for R and Python, source codes and links to census data are provided in a notebook format to enhance experience with running the software. The code illustrates different aspects of using geospatial analysis: (1) creation of choropleth (thematic) map which depicts estimate of stroke cases per post codes; (2) use of map to help define service regions for rehabilitation after stroke.

Results: Choropleth map showing estimate of stroke per post codes and service boundary map for rehabilitation after stroke. Conclusions The examples in this article illustrate the use of a range of components that underpin geospatial analysis. By providing an accessible introduction to these areas, clinicians and researchers can create code to answer clinically relevant questions on topics such as service delivery and service demand.

Keywords: geospatial, software, data, review, stroke, emergency clot retrieval

1. INTRODUCTION

Endovascular clot retrieval (ECR) and thrombolysis enables reperfusion following ischemic stroke and results in dramatic reversal of neurological deficit in selected patients (1–6). The publication of the DEFUSE3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) and DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) trials potentially pushed the boundary for performing ECR in a small set of patients to 24 h (7, 8) and thrombolysis to 9 h (6). ECR treatment requires specialist centers with 24 h staffing by skilled stroke teams and interventional radiologists with unrestricted access to angiography suites. Key decisions for governments and policy makers include: how many centers are required to service a specified area, how to identify redundant centers, where should the centers be placed and what is the expected load on the centers (9). Many factors influence the final choice, including the availability of trained interventional neuroradiologists (INR), the number of cases required for INR to retain skills, and costs.

Related to the above considerations is the issue of transport model. One proposed model is direct transport to mothership (ECR hub) whereby ambulance bypass the smaller hospitals including those which are thrombolysis capable and take the patient to directly to the ECR hub (10, 11). The alternative model is the "drip and ship" model whereby patients are brought to the nearest thrombolysis center for advanced imaging and trigging on the need for thrombolytic drug and or ECR. A drawback to the drip and ship model is that there is an additional 99 minutes delay related to a second transfer of the case with large vessel occlusion (LVO) to the mothership (12). Investigators recently proposed inclusion of speed of delivery of thrombolysis as an additional consideration (11). Identification of patients for ECR at the pre-hospital level requires either the use of LVO scale or mobile stroke unit (MSU). Before LVO scales can be used in the field, the impact from its use on ECR hub loading (handling of large volume of ECR and non-ECR cases) has to be tested.

In the writing of this introduction, we have asked several data scientists (software engineers) to contribute the introduction to geospatial analysis for clinicians and other citizen scientists aspiring to work in the field. Alternatively, a deeper understanding of these geospatial methods will enable clinicians to collaborate with other researchers or citizen scientists on models to improve local stroke service. Both codes and data are provided so that once *R* and *Python* softwares are installed, the scientist can copy and paste the example codes to test run. These softwares typically involve relatively steep learning curves and as such instructions for running the softwares are provided; please see the more extensive codes and data on our github address https://richardbeare.github.io/GeospatialStroke/. The examples provided here are not exhaustive and are intended to stimulate creative use of these geospatial tools. The two examples we present are a choropleth (thematic map) and a service catchment basin estimation. A choropleth is a thematic map display in which regions are colored by a measure of the region. We use demographic and boundary data from the Australian Bureau of Statistics and incidence data from the NEMESIS (13, 14) study to estimate stroke cases per postcode and display the result on an interactive map. The service catchment basin estimation involves a Monte-Carlo simulation of patients attending a rehabilitation service of 3 hospitals. The catchment basin of each hospital is the region that has lower travel time to that hospital than any other. Catchment basins can be combined with incidence data to estimate load on rehabilitation centers. The data can be used to explore scenarios, such as the removal or addition of service centers.

2. GEOSPATIAL ANALYSIS

Geospatial analysis or modeling of spatial data has traditionally been the domain of *geographic information systems (GIS)* specialists, employing commercial software and data products. Recent years, however, have seen the development of open source tools and free or low cost web services, such as Google Maps, that make geospatial analysis accessible and feasible to the non-specialist citizen scientist. In this article we introduce a family of computational techniques and services, collectively termed geospatial analysis tools, that can be applied to a range of questions relevant to stroke services. The codes used here are for two free and open source software environments—*R* and *Python*. Geospatial analysis can also be performed with Matlab (10); this software is not free and will not be discussed further. Geospatial analysis tools allow manipulation and modeling of geospatial data. These tools, data, and modeling techniques have a long track record in the quantitative geography, city and regional planning, and civil engineering research literatures. Geospatial data, in the context of stroke research, includes the location of patients and treatment centers, routes through the road network linking patients to treatment centers, geographic and administrative region boundaries (e.g., post codes, government areas, national boundaries) and disease incidence and demographic information associated with such regions.

2.1. Geospatial Frameworks

In geospatial analysis, the location of a data point on the Earth's surface is referred to in terms of longitude and latitude. In practice, longitude is the X axis and latitude is the Y axis. More complex data, such as national boundaries or administrative or postcode boundaries consist of sets of points connected together in defined orders, typically to produce a closed shape. Other structures, such as road networks, are also constructed using sets of points and include other types of information, such as speed limits, travel direction etc. A geospatial framework provides mechanisms for representing, loading, and saving geospatial data and performing fundamental mathematical operations. For example, the simple features (sf) (15) package, on which our R examples are based, provides structures to represent all manner of shapes and associate them with non-spatial quantities, perform transforms between coordinate systems, display shapes, compute geometric quantities like areas and distances and perform operations like intersections and unions. The equivalent Python framework is the geopandas package that provides a geospatial extension to standard data frames. A key emerging subdomain of geospatial analysis is spatial network analysis. Several open-source packages now exist for modeling and analyzing spatial networks, such as urban street networks, including dodgr for R (16) and OSMnx for Python (17).

2.2. Sources of Regional Data

The examples below use postcode boundary data available from the Australian Bureau of Statistics (the codes for performing this task are available in the **Supplementary Material** or on the website https://richardbeare.github.io/GeospatialStroke/). It is common for boundaries used in reporting of regional statistics to be available in standard file formats from the reporting bodies or central authorities along with the reported statistics. The regional demographics measures, often derived from national census data, also represent an important source of information for researchers, including age, sex, income, ethnicity etc. For example, in the US, key data sources on sociodemographics and the built environment include the Census Bureau's decennial census (18) (a complete enumeration at fine spatial scales but coarse, decadal temporal scales), American Community Survey (19) (a survey with annual temporal scales, but often fairly large standard errors at small spatial scales due to the sample size), and TIGER/Line shapefiles (20) of tract, municipal, and urbanized area boundaries. A comprehensive repository of US road network models at regional and municipal scales is available on the Harvard Dataverse (21). Additional regional data are frequently available from municipal, state, county, or metropolitan governmental agencies. Demographic data for countries in the European Union are provided by Eurostat (22). This includes time series data from several years to decades on economics, demography, infrastructure, health, traffic, and more of the EU (23). Geographic data for the EU is available through the Geographic Information System of the COmmission (GISCO), part of Eurostat. Similar levels of demographic data are available from France through INSEE (24), Germany through Destatis (25) and, Switzerland through (26). There are a number of European sources of geospatial data (27–29).

TABLE 1 | Steps 1-4 in computation of interactive display of choropleth of estimated stroke incidence. R code listings from the demonstration scripts is included.

1 **Loading census and boundary data: The followings are snippets of code and are provided here to understand the commands. To create the maps below, please download the full code (https://github.com/richardbeare/GeospatialStroke/archive/master.zip).** Data from the 2016 Australian National Census is available from the Australian Bureau of Statistics, and copies are included with the code at the link above. The two parts of the data are the national postcode boundaries (loaded with the sf::read_sf command) and the demographics, by postcode, for the state of Victoria, loaded with the readr::read_csv command.

```
postcodeboundariesAUS <- sf::read_sf(here::here("ABSData",
            "Boundaries",
            "POA_2016_AUST.shp"))

basicDemographicsVIC <- readr::read_csv(here::here("ABSData",
            "2016 Census GCP Postal Areas for VIC",
            "2016Census_G01_VIC_POA.csv"))
```

The *here::here*() function provides a robust way of locating files within projects.

2 **Geocoding hospital location:** The coordinates of the hospital of interest, Monash Medical Centre, are determined by geocoding the hospital address, using the tmaptools::geocode_OSM command. This command uses the OpenStreetMap Nominatim geocoding service.

```
MMCLocation <-
  tmaptools::geocode_OSM("Monash Medical Centre, Clayton, Victoria, Australia",
  as.sf=TRUE)
```

3 **Combine demographics and spatial data**. An important feature of the simple features (R) and geopandas (Python) frameworks is the ability to combine spatial data, such as postcode boundaries, with associated statistical summaries (stroke count, demographics etc). This step uses the right_join function to attach the demographic data to the set of postcodes. The right_join performs two tasks - attaching the demographics data and discarding the postcodes for which we don't have demographics data (i.e., those from other states of Australia).

```
basicDemographicsVIC <- right_join(postcodeboundariesAUS, basicDemographicsVIC,
                                   by=c("POA_CODE" = "POA_CODE_2016"))
```

4 **Compute per-postcode stroke incidence:** A column representing stroke incidence per postcode is added to the demographics table. The computation uses incidence data published by the NEMISIS (13) study to provide rates per 100,000 for various age ranges. The demographics data also includes population by age range, allowing computation of stroke incidence as a weighted sum of population columns. Names such as Age_55_64_yr_P refer to the name of a column in the demographics table.

```
basicDemographicsVIC <- mutate(basicDemographicsVIC,
                              Age_0_24_yr_P = Age_0_4_yr_P + Age_5_14_yr_P +
                                Age_15_19_yr_P + Age_20_24_yr_P)
basicDemographicsVIC <- mutate(basicDemographicsVIC, stroke_count_estimate = (Age_0_24_yr_P  * 5 +
    Age_25_34_yr_P * 30 +
    Age_35_44_yr_P * 44 +
    Age_45_54_yr_P * 111 +
    Age_55_64_yr_P * 299 +
    Age_65_74_yr_P * 747 +
    Age_75_84_yr_P * 1928 +
    Age_85ov_P     * 3976) / 100000)
```

TABLE 2 | Steps 5-7 in computation of interactive display of choropleth of estimated stroke incidence.

5 **Compute distance from postcode to hospital:** We create a column containing the distance from each postcode to the hospital of interest using the sf::st_distance function, which automatically accounts for complexities, such as the curvature of the earth. We also set the units of quantities to km. We then use the distance in a simple, static, choropleth to verify the operation. Cool colors, corresponding to small distances are in the expected location.

```
basicDemographicsVIC <- sf::st_transform(basicDemographicsVIC,
                                   crs = sf::st_crs(MMCLocation))
basicDemographicsVIC <-
   mutate(basicDemographicsVIC,
          DistanceToMMC=units::set_units(st_distance(geometry,MMCLocation)[,1], km))
```

6 **Discard remote postcodes:**. Postcodes further than 20 km from the hospital are discarded by filtering the data based on the newly calculated distance column.

```
basicDemographicsMMC <- filter(basicDemographicsVIC, DistanceToMMC < set_units(20 km))
```

7 **Interactive display of the result:** Finally, an interactive map is created using the tmap packagec(R). The postcode boundaries are colored according to our estimated stroke count and overlaid on a zoomable map provided by OpenStreetMap. Any column in our dataset can be visualized in a similar way. A number of useful interactive features are available in this style of display, including popup displaying the postcode when hovering the mouse over a region and more detailed information available when clicking on a region.

```
library(tmap)
tmap_mode("view")

MMCLocation <- mutate(MMCLocation, ID="Monash Medical Centre")
basicDemographicsMMC <- mutate(basicDemographicsMMC, Over65 = Age_65_74_yr_P + Age_75_84_yr_P + Age_85ov
    _P)
tm_shape(basicDemographicsMMC, name="Annual stroke counts") +
  tm_polygons("stroke_count_estimate", id="POA_NAME", popup.vars=c("Cases"="stroke_count_estimate"),
      alpha=0.6) +
  tm_shape(MMCLocation) + tm_markers() +
  tm_basemap("OpenStreetMap")
```

2.3. Geocoding and Reverse Geocoding

Location information, such as a patient's home address, is often available as a street address, rather than coordinates (a longitude/latitude pair). However, operations such as plotting addresses on a map require coordinates. Geocoding is the process of converting an address to a coordinate pair. Reverse geocoding converts a coordinate pair to an address. Coordinates are useful in many other types of computation, as we shall see in the examples below. There are two common approaches to geocoding and reverse geocoding. The most ubiquitous is via web services such as Google Maps. Other services, such as OpenStreetMap's Nominatim web service and OpenCage (https://opencagedata.com/), provide similar capabilities and all can be queried in an automated way from R and Python (30). The other approach is via a local database of geocoded addresses. One example, for Australia, is the PSMA (formerly Public Sector Mapping Agencies) address database available in an R queryable form. A local database allows many high speed queries, but is often less flexible in terms of query structure than the web services. Web services are discussed in more detail below.

2.4. Distance and Travel Time Estimation

A key part of a number of studies cited above is the estimation of travel time between patient and treatment center. The popularity of personal navigation systems in smartphones has driven the development of extremely sophisticated tools to estimate the fastest route between points. One of the best known, Google Maps[1], uses a combination of information about the road network, historic travel time data derived from smartphone users and live information from smartphones. The travel time estimates are thus sensitive to time of day, weather conditions and possibly traffic accidents. Google, and other web services for travel time estimation, can be queried in a similar fashion to the geocoding services. It is also possible to create a local database to represent the road network, allowing more rapid querying, but losing some of the benefits of traffic models.

2.5. Visualization

Two forms of visualization are used in the following examples - static and interactive. Static maps are required for printed reports and typically present a carefully selected view. Interactive maps allow exploration of a data set, via zooming and toggling of overlays. Interactive maps often use web services to provide the background map "tiles," over which data is superimposed. Different interactive web services specialize in different types of display. Some tools produce static and interactive displays in very similar ways.

2.6. Introduction to Web Services

Web services providing various forms of geospatial capabilities are a crucial component of the geospatial analysis tools now

[1] the two APIs involved are the directions api and distance api.

available to researchers. Web services deliver what used to be complex and specialized information products to the general public. Geocoding and travel time estimation are two common examples that have already been discussed. Other capabilities include delivery of tiled maps (such as the Google Maps display), street network and building footprint data (such as from OpenStreetMap), and census data on sociodemographic or built environment characteristics (such as from the US Census Bureau).

2.6.1. Application Programming Interfaces (API)

Web services such as Google Maps are accessible via an API. The API allows software tools, such as *R* or *Python*, to make requests to the web service and retrieve results. Thus, if we consider the Google Maps example, not only can a user access a map query for an address via a web browser, but a program can submit the same request. Furthermore, a program can submit a series of automated requests. For example, given a list of addresses, it is relatively simple to generate an R or Python procedure to geocode all of them via a web service. Many

TABLE 3 | Steps in computation of catchment basin and case load for rehabilitation centers.

The first three steps are as described in **Table 1**, with multiple addresses being geocoded in step 2.

4 **Compute distance to each service center from each postcode:** A study area is generated by computing the distance to each service center from each postcode and retaining only postcodes within 10 km of a service center

5 **Randomly sample addresses in postcodes:** A set of random addresses is created for each postcode by randomly sampling a database of addresses. The number of addresses sampled depends on the sampling approach and the subsequent computations, but if local methods are used it is feasible to use large numbers of samples. In this case we use 1,000 per postcode. Lower numbers would be appropriate if subsequent computations required charged web services.

```
library(PSMA)
samplePCode <- function(pcode, number) {
  d <- fetch_postcodes(pcode)
  return(d[,.SD[sample(.N, min(number,.N))], by=.(POSTCODE)])
}

randomaddresses <- map(basicDemographicsRehab$Postcode,
                       samplePCode,
                       number=addressesPerPostcode) %>%
             bind_rows() %>%
             sf::st_as_sf(coords = c("LONGITUDE", "LATITUDE"),
                          crs=st_crs(basicDemographicsRehab),
                          agr = "constant")
```

6 **Display sample addresses and postcodes:** Display the samples in a map form to verify that the distribution matches expected population distribution - i.e., that there are lower densities in rural areas, and that the study area is appropriate.

7 **Create a street network database:** In this example we are employing a local approach to travel time estimation. The first step is to fetch a road network database from OpenStreetmap and convert to a network form for analysis. There are a number of tricks discussed in the online document that reduce the size of the download by exploiting knowledge of the study area.

```
library(dodgr)
dandenong_streets <- dodgr_streetnet (bounding_polygon, expand = 0, quiet = FALSE)
```

8 **Estimation of travel time:** travel time from each address to each service center is then computed using the dodgr::dodgr_dists function, which is optimized to rapidly compute large sets of pairwise distances.

```
net <- weight_streetnet (dandenong_streets, wt_profile = "motorcar")
nodes <- dodgr_vertices (net)
fromIDX <- match_pts_to_graph (nodes, fromCoords, connected = TRUE)
from <- unique (nodes$id [fromIDX])
to <- nodes$id [match_pts_to_graph (nodes, toCoords, connected = TRUE)]
d <- dodgr_dists (net, from = from, to = to)
```

9 **Address-based catchment basins:** Each address is assigned to a service center by identifying the center with the shortest travel time. A view using a scatter plot of points colored by destination is then created to verify the result.

10 **Polygon catchment basins:** We convert the pointwise classification to a polygon representation using a Voronoi tessellation approach. The Voronoi tessellation of a set of points is a set of polygon catchment basins, one basin for each point. However the definition of "closer" for the Voronoi basins is based on Euclidean distance rather than road network distance or travel time. The Voronoi polygons are from addresses assigned to the same service center are then merged to create the polygon representation of the service center catchment, which can be displayed.

11 **Estimate caseload per center:** The catchment areas can be used in conjunction with the per postcode demographics to make estimates. We use our per postcode stroke estimate procedure from the previous example as a basis for determining the number of rehabilitation cases (a simplification for illustration purposes). The sampled addresses are the basis for this computation, with the proportion of sampled addresses from a postcode assigned to a service center corresponding to the proportion of cases from that postcode attending the center.

APIs such as Google Maps are commercial products and thus charge for use, although the use is often free for small volumes (typical limit is 2,500 queries per day). The combination of these factors tends to mean that many APIs require somewhat complex setup, typically via signup and creation of keys. Terms of use may evolve over time, with charging being introduced, possibly leading to a need to enter credit card details (necessary for Google Maps API). We have endeavored to create

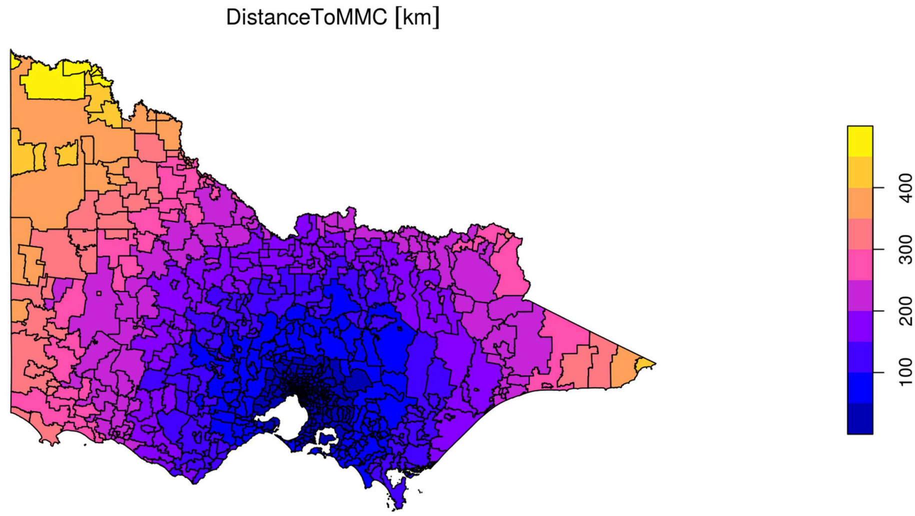

FIGURE 1 | Visualization of straightline distance calculation from every postcode in the state to Monash Medical Centre. Static visualization created with *tmap*.

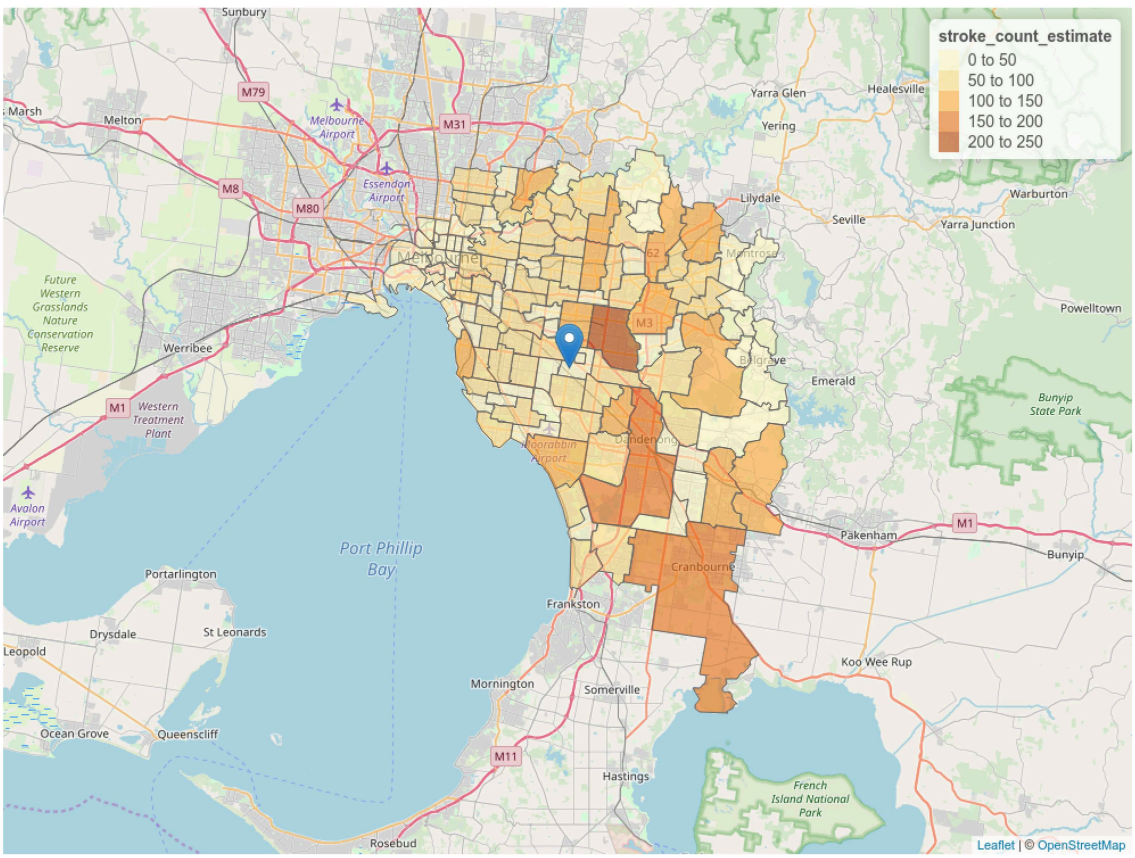

FIGURE 2 | Choropleth of stroke case load estimate. Postcodes are colored according to estimation of stroke cases derived from demographic data. Screenshot of interactive visualization created with *tmap*.

examples that do not require keys, simplifying getting started (tmaptools and OpenStreetMap). However, some extensions have been included that do require keys. These are described in **Supplementary Material**.

2.6.2. OpenStreetMap (OSM)

OSM (https://www.openstreetmap.org/) is a service collecting and distributing crowdsourced geospatial data. Many useful OSM services are available without API keys, and it is thus the platform of choice for examples in this paper. OSM is also unusual in that it allows access to underlying geospatial structures, such as road networks, rather than images generated from those structures. This capability is used to estimate travel time.

2.6.3. Access to the Examples

The examples are available in their source code form from https://github.com/richardbeare/GeospatialStroke/archive/master.zip. "Live" versions and instructions are available at https://richardbeare.github.io/GeospatialStroke/index.html and can be viewed in conjunction with the methods section. The description focuses on the *R* versions of the examples. Code is visible in the shaded boxes, while output of the code, such

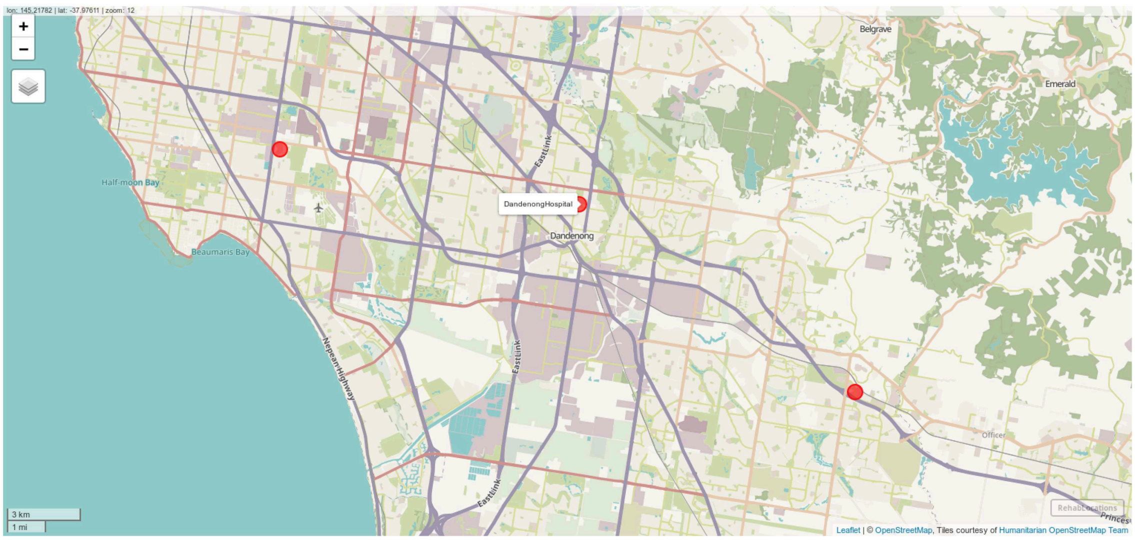

FIGURE 3 | Locations of the three rehabilitation centers determined by geocoding. Screenshot of interactive visualization created with *mapview*.

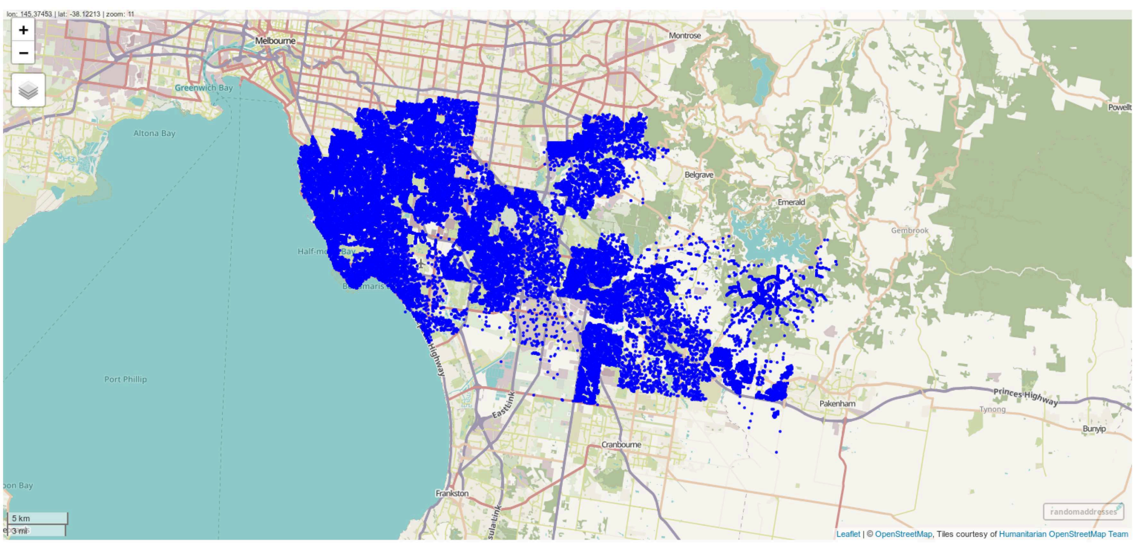

FIGURE 4 | Randomly sampled addresses within the postcodes of interest. One thousand addresses per postcode were sampled, and the differing population density across the postcodes of interest is clearly visible. Screenshot of interactive visualization created with *mapview*.

as maps, are displayed immediately after the code. *Python* versions are provided and implement equivalent steps. Details on downloading and running the examples are available in **Supplementary Material** and at the web site.

3. METHODS

The key sections of code used in the methods are presented and described in tables in this article. These pieces of code are not intended to be executed in isolation, and are best appreciated in the complete examples (both code and data), which are too long to include directly in the article, but are available for download, as described in section 2.6.3.

3.1. Example 1: Choropleth to Visualize Estimated Stroke Numbers

3.1.1. Overview

We demonstrate accessing and using different data sources. The first is Australian Bureau of Statistics census data provided at the postcode level for population information, stratified by age, as well as postcode boundary information. The second data source is incidence data from the North East Melbourne Stroke Incidence Study (NEMESIS) (13). This is combined with the first dataset

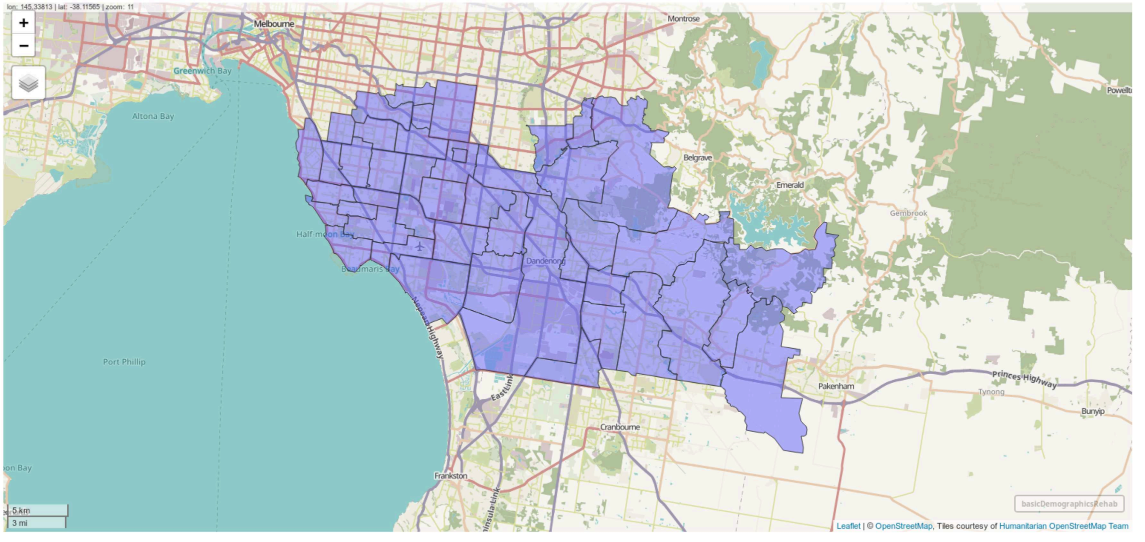

FIGURE 5 | Boundaries of postcodes with centroids within 10 km of one of the rehabilitation centers. Screenshot of interactive visualization created with *mapview*.

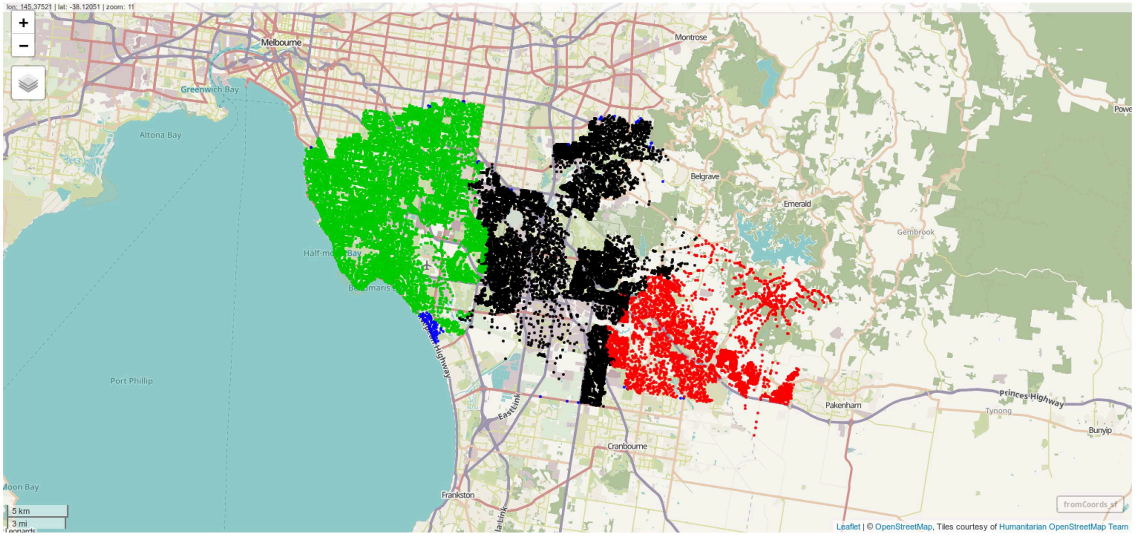

FIGURE 6 | Sampled address colorcoded according to nearest destination, with distance to destination computed through the street network. Screenshot of interactive visualization created with *mapview*.

to estimate per-postcode stroke incidence. We demonstrate geocoding by finding the location of a hospital delivering acute stroke services, and then display postcodes within 15 km, coloring each postcode by estimated stroke incidence. The steps involved are described in **Tables 1**, **2**.

3.1.2. Example 2: Service Regions for Stroke Rehabilitation

In the second example we demonstrate the idea of estimating catchment basins for a set of three service centers (network comprising three rehabilitation hospitals servicing a hospital with an acute stroke service). The idea can be easily extended to more service centers. A catchment basin, or catchment area for a service center is the region that is closer to that service center than any other. The definition of "closer" is critical in this calculation, with travel time through the road network being a useful measure for many practical purposes. The approach used in this example involves the sampling of random addresses within a region of interest around the service centers, estimation of travel time from each address to each service center, assignment of addresses to the closest service center, combination of addresses based on service center to form catchment areas. The catchment areas can then be used to estimate loadings on service centers. The steps involved are described in **Table 3**.

4. RESULTS

The results of the two examples described above are a combination of source code and data and the output from the code. The output consists of visualizations of spatial data and estimates of rehabilitation loadings.

Complete versions of the examples are illustrated online at https://richardbeare.github.io/GeospatialStroke/index.html. A zipfile containing the complete data and code used to create the results can be downloaded from https://github.com/richardbeare/GeospatialStroke/archive/master.zip, and these two resources are the recommended starting point for readers interested in reproducing the results in this paper and getting started with experimentation with the ideas presented.

The key points of the examples are described in tables in the methods sections. However these points are best appreciated in the context of the complete examples.

4.1. Example 1: Choropleth to Visualize Estimated Stroke Numbers

Spatial data, as displayed by an *R* session, is illustrated in **Tables S1, S2**. **Table S1** shows the hospital coordinates determined via geocoding, while a subset of the combined spatial, demographic and estimated stroke count data is illustrated in **Table S2**. A visualization of straight-line distance between each postcode and the hospital, useful for verifying the calculation is sensible, is illustrated in **Figure 1**. Finally, **Figure 2** provides a screenshot of the interactive choropleth featuring postcodes in the vicinity of the hospital colored by estimated stroke case load. The display can be exported as a web page and viewed interactively, with the ability to pan and zoom and switch display layers on and off.

4.2. Example 2: Service Regions for Stroke Rehabilitation

Results of geocoding rehabilitation center addresses is shown in **Table S3** with the corresponding visualization in **Figure 3**. A small selection of random addresses is available in **Table S4** and the complete set is visualized in **Figure 4**. Boundaries of postcodes of interest are shown in **Figure 5**. **Figures 6–8** show addressed-based, polygon-based and road-based views of

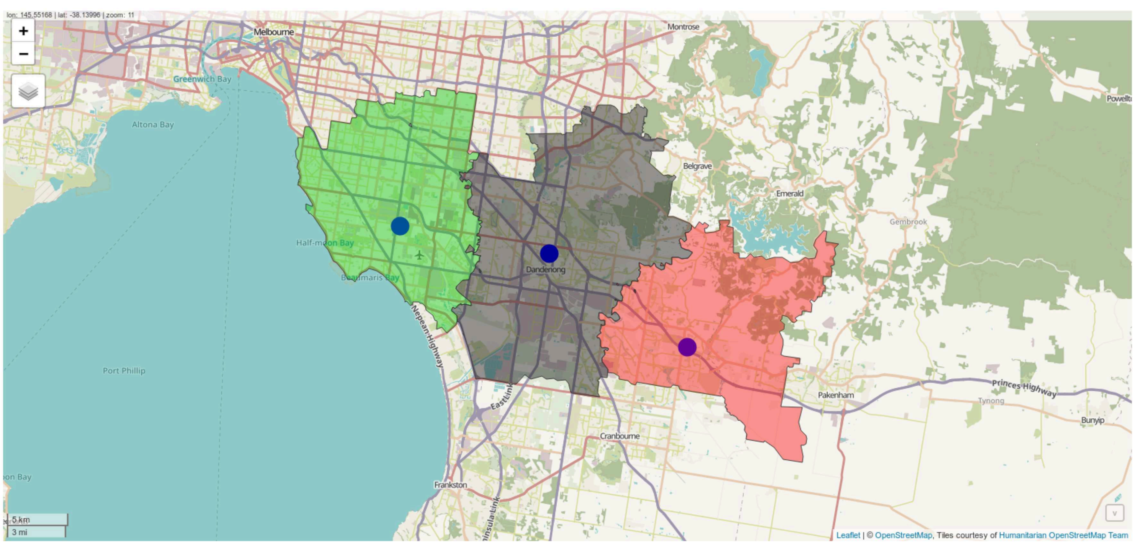

FIGURE 7 | Polygon representation of rehabilitation center catchment zones. Screenshot of interactive visualization created with *mapview*.

the computed catchment basin. **Figures 9**, **10** show alternative visualizations of travel time using a hexagonal height map and a color coded road network. Finally, allocation of random addresses to rehabilitation centers and estimated case loads per catchment center are available in **Tables 4**, **5**.

5. DISCUSSION

There are many potential advantages to including geospatial variables such as location of patients and travel times to treatment centers when analyzing performance of, or modeling

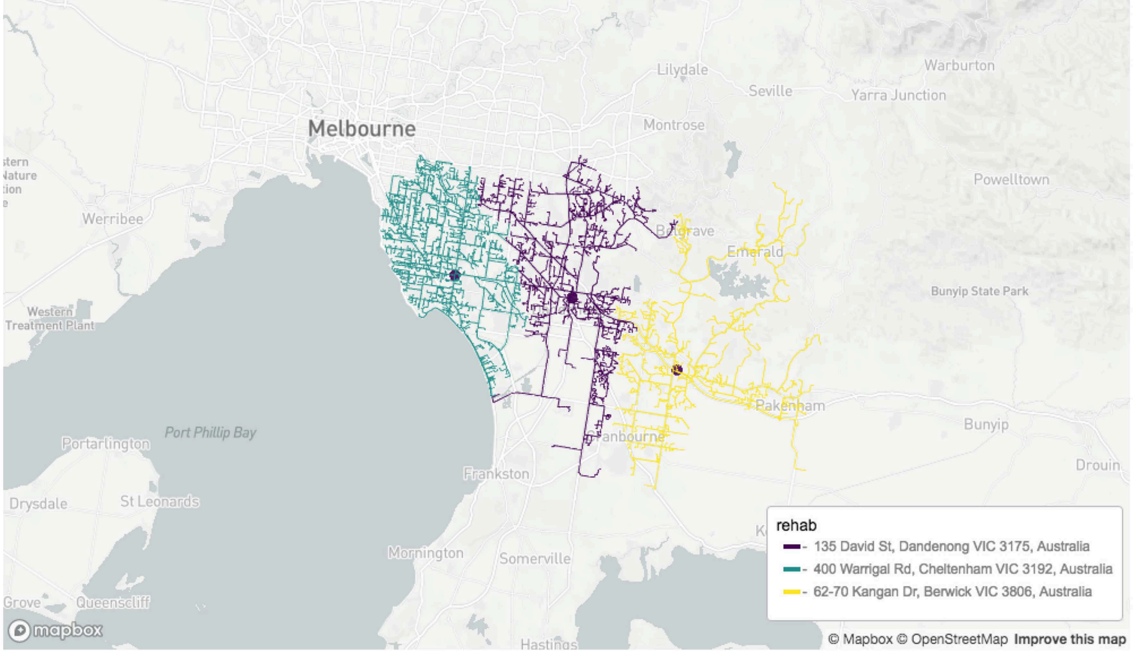

FIGURE 8 | Road network-based visualization of catchment zones for rehabilitation centers. Screenshot of interactive visualization created with *mapdeck* (API key required).

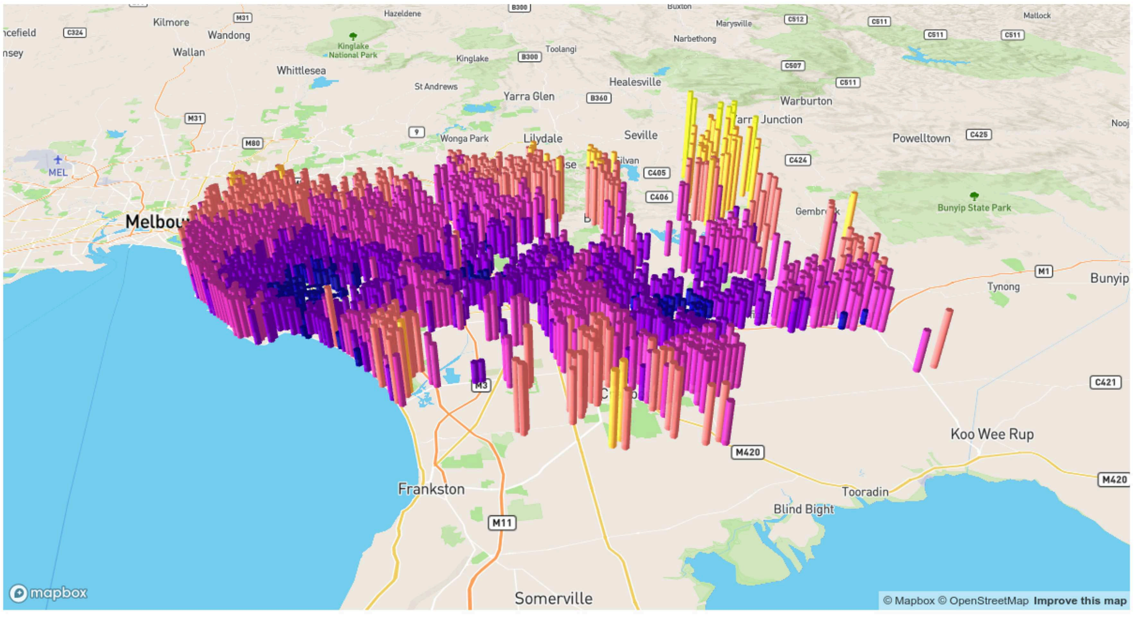

FIGURE 9 | Alternative visualization of distances from random addresses to rehabilitation centeres. Screenshot of interactive visualization created with *mapdeck* (API key required).

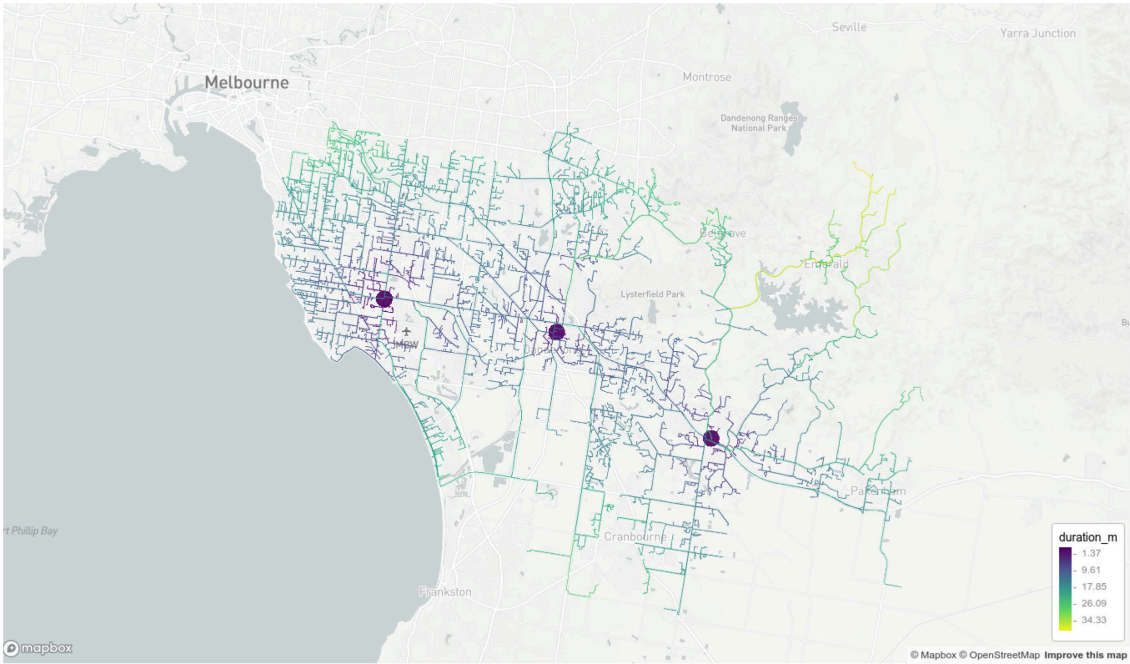

FIGURE 10 | Road network visualization of travel times from random addresses to rehabilitation centeres. Screenshot of interactive visualization created with *mapdeck* (API key required).

TABLE 4 | The proportion of randomly sampled addresses allocated to each rehabilitation center via the distance calculation.

Destination	Total	Percent
CaseyHospital	6059	13.78
DandenongHospital	14184	32.26
KingstonHospital	23720	53.95

TABLE 5 | The estimated case load per center, based on combination of per postcode prediction based on demographics and assignment based on distance calculations.

Destination	Total	Percent
CaseyHospital	289	10.67
DandenongHospital	882	32.55
KingstonHospital	1538	56.77

stroke treatment pathways. The ability to accurately model parts of the treatment pathway is important when fairly allocating limited resources, optimizing the placement of those resources, forecasting changes in loading in response to change in population distribution and investigating how to best utilize new technology or treatment options. In this article we have introduced some of the fundamental geospatial analysis components and provided reproducible examples using those components in a form that we hope will reduce the steep learning curve for researchers new to the area. In the writing of this paper, we heeded the call from this special issue of Frontiers in Neurology to provide source codes and enable both stroke researchers and "... citizen scientist to explore ideas in transportation and access to stroke therapy." Recent years have seen increasing use of geospatial analysis techniques, similar to those explored in this paper, in stroke research as well as other health related areas. Two scenarios, with different spatial scales, for provision of acute stroke services are explored in Allen et al. (31) via an optimization framework, where the costs being optimized are derived from geospatial measures, including travel time. Implications of new technology (MSU) for rural patients is discussed in Mathur et al. (32) and urban application of the same technology is quantitatively analyzed in Phan et al. (33), with analysis exploiting travel time derived from web services to estimate deployment boundaries. Rather than providing further examples in acute stroke services of which are published in his special topic (31–33) we had provided examples here in terms of rehabilitation service provided by 3 hospitals attached to an ECR hub (**Figures 3–10**). Fair distribution of load across the hospital network is possible while allowing the patients and family unit in close contact, in keeping with the idea of patient centrad design. These studies discussed here were conducted to inform decisions under specific assumptions and in relation to individual urban environments (i.e. specific cities). However, they share common analytical ideas and data, namely geospatial analysis tools of the form explored in this paper. Use of these frameworks allow relevant research to be extended to different urban environments and extended as new assessment tools or treatment or transport options become available. For example, the tools described in this paper allow a researcher and citizen scientist to explore how the models relate to their own city as the key data, travel time and center location, can be collected easily from web services (10, 11) Furthermore, the analysis could be modified to investigate the effect of a new LVO assessment tool on decision making (34). The focus of discussion thus far has been on acute stroke services, however there are applications in many other health areas. For example, effects of traffic conditions on staff recall times for ST elevation myocardial infarction patients has been explored using similar approaches (35). Finally, geospatial analysis can be adapted to evaluation of brain health as seen in a recent study of the associations between brain measures and a neighborhood walkability index computed from geospatial data (36).

5.1. Limitations

In this project, we have provided examples in urban setting only. Modeling of transport in non-urban rural setting can be complex as it may have to take into account air transport.

A limitation of the current work in which the traffic model is based on Google Maps API, is that it does not take into account population growth and change in road network. In a paper in this journal, strategic transport model was used to assess stability of the geospatial model over time (37). Further geospatial analysis is only one component of a complex equation governing decisions on optimal centralized models for acute stroke therapy. As alluded to earlier in the article, the equation would also involve hospital capacity, availability of interventional neuroradiologists and stroke neurologists. For example, in the State of Victoria, Australia there are currently 13 certified interventional neuroradiologists with the majority of these currently in the two designated clot retrieval hubs http://www.ccinr.org.au/register (accessed 23/3/2019). As such adding a third hub in this centralized acute stroke therapy model would require acquisition of additional personnel. The choice of a model such as direct transfer to "mothership" for all patients would require modeling to estimate its effect on capacity of "mothership" to handle evaluation of all stroke cases since 84% of acute stroke cases do not go on to ECR (38). These types of modeling, such as discrete event simulation and agent-based modeling, were not covered in this introduction to software for geospatial analysis. An alternative strategy to support the "mothership" model is the use of bedside tools to screen patients for LVO (34). These tools have not yet been rigorously and prospectively tested in the field, nor has the impact of these tools on hospital case load been tested.

6. CONCLUSION

Computational frameworks facilitatinig analysis of geospatial data are now more accessible than ever before due to the combination of open source software tools, increasing availability of geospatial, demographic and other relevant health data from government and administrative bodies and a plethora of web services offering advanced geospatial data products. These tools are extremely powerful and flexible and offer the potential to address many important questions in stroke treatment. We hope this paper provides a useful introduction to researchers wanting to utilize spatial data. We invite the reader and citizen scientist to take the next step.

DATA AVAILABILITY

Publicly available datasets were analyzed in this study. The data and code can be found here: https://github.com/richardbeare/GeospatialStroke/archive/master.zip.

AUTHOR CONTRIBUTIONS

RB, TP, MP, NT, DC, MS, and GB contributed to the research plan. RB, GB, MP, MS, and DC wrote the code. RB, TP, NT, GB, and MS wrote the manuscript and provided critical reviews.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00743/full#supplementary-material

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