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Justin Joseph April 10, 2023

Young Adults with Stroke: A Scoping Review of Epidemiology, Sequelae and Rehabilitation Needs

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
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Abstract

Young Adults with Stroke: A Scoping Review of Epidemiology, Sequelae and Rehabilitation Needs

By Justin Joseph

Background: Worldwide 80 million individuals have experienced a stroke in their lifetime, and 10% of affecting young adults.[1, 2] Incidence levels of stroke in young adults continues to rise; 36% in person aged 35-44 and 27% persons aged 18-34 between the years of 2003 and 2012.[3, 4] Observable racial and ethnic disparities in outcomes within YAS (Young Adult Stroke) population.[1, 3-6] The objective of this scoping review is to synthetize the literature and summarize the epidemiological factors, clinical characteristics, and utilization of post-acute care services among YAS.

Methods: Peer-reviewed manuscripts from PubMed, PsycINFO, Web of Science, EMBASE and CINAHL with search terms "young," "stroke" and "cerebrovascular accident" were retrieved. Studies between 2003-2021 and including individuals with stroke between ages of 18-65 were included. To adhere to PRISMA guidelines, two reviewers independently screened each abstract and full-text article. The search yielded 11,858 articles, 5,097 were excluded as duplicates, 3,491 articles were excluded during title and abstract screening leaving 2,347 articles to be considered in the full-text review. A total of 187 articles were included following full text review.

Results: The review included a total of 1,093,366 YAS, ranging in age from 18 to 65 years. The mean age of YAS was 37 years (n=127 studies). The definition of young adults varied across studies, with 43% studies defining young adults as18 to 50 years old, 26% studies using a range 18-45 years old, and 12% studies defining young adults as 30-65 years old. The mean National Institutes of Health Stroke Scale (NIHSS) score was 6.6 (n=12 studies). The average mortality rate among YAS was 1.4% (n=19). The mean length of stay was 10 days (n=7). Minimal reporting of stroke incidence across racial groups found YAS were 61% white, 23% Black, 10% Hispanic, 5% other, 1% Asian/Pacific Islander, and less than 1% Native (n=14). Risk factors unique to YAS reported oral contraceptives (n=4), hyperhomocysteinaemia (n=4) and patent foramen ovale (n=6). Post stroke sequelae among YAS included impairments with motor, cognition (12%; n=21), anxiety (40%; n=7), and depression (40%; n=14). Functional outcomes were reported using a modified Rankin Score (mRS), where 58% of YAS had a mRS 0-2 and 42% had a mRS >2 (n=21). Unaddressed psychosocial needs led to feelings of fear and isolation. Lastly, post-acute care discharge disposition and return to work were reported with 56% of YAS discharged home and 63% of YAS returned to full-time work (n=19).

Conclusions: Unique risk factors, increasing incidence and prevalence, racial disparities, unknown etiologies, lack of understanding of fiscal impact, and outcomes are all factors contributing to the importance of understanding YAS. Future studies including YAS, describing their demographics and clinical make up adequately (racial/ethnic background, age stratification, etiology, unique risk factors), and develop and test interventions and services focused for YAS based on their unique needs and risk factors.

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Young and Restless Stroke/TBI Support Group of Atlanta

Table of Contents:

Motivation:

This project's motivation is underlined through the methodological approach of community-based participatory research. I started my journey by volunteering and now currently leading one of the only young adult stroke and traumatic brain injury support groups in Atlanta, The Young and the Restless of Atlanta. Through my participation through this program, I was able to hear experiences, real emotions, and the true burden of disease that occurs for the lives of young stroke survivors. It is one thing to research a disease, but it is another to understand their experiences from our community members, our neighbors and real survivors' voices. Our discussions have led to the motivation of a research question that is specific to young adults because of the specificity and uniqueness of this population. For example, the story of our co-leader and Community leader Roger Braithwaite paints a picture of a husband, business executive and most importantly to him a father of two amazing young men. He survived two ischemic strokes that has changed the course of his life forever; however, has taken these experiences and inserted them into an opportunity to change the course of many others in his community by helping start this support group. The conversations we discuss in support group range from estate planning, music therapy, therapeutic gardening as well as innovative technological devices aiding in the rehabilitation of survivors. In fact, the variable of invisible deficits was directly motivated by the conversations through our survivors. I learned firsthand the effect of fatigue, marital stress, attitudes toward return to work and the feelings towards childcare played an integral role in the lives of young stroke survivors. Therefore, I took these stories, asked more questions and went on the search for answers. I believe it is imperative as a young researcher that our research transcends the classroom, conference, or journal but rather more importantly gives back to our community, our neighbors, and the individuals this disease has

touched. I'm proud to say that our research is being impacted by community members and their voices are being heard and researched - I take great pride in being able to communicate that through this opportunity.

Introduction:

Stroke impacts 80 million people worldwide, with studies estimating approximately 10% of all strokes affect adults under 50 years old (Ekker et al., 2018; Maaijwee et al., 2014). Although the total incidence of stroke across all ages has decreased, stroke in the young adult population has increased between 1998 to 2010 by at least 23% and between 2003 and 2012 there has been a 27% increase in acute stroke incidence in persons 18-34 and a 36% increase in persons 35-44 (Ekker et al., 2019; George et al., 2017). Furthermore, the incidence rate ratio between 2014-2015 vs 2005-2006 among 18-45 yrs. is 1.62 (95% CI 1.10-2.40), and among 18-55 is 1.38 (95% CI 1.12-1.71) (Cabral et al., 2017). In fact, 38% of hospitalizations for stroke are among individuals less than 65 years old (Jackson & Chari, 2019). Additionally, in 2013 there were also 1.5 million deaths attributed to stroke globally in individuals between 20-64.(van Alebeek et al., 2018). Racial disparities are evident among stroke where African Americans are four times more likely to have an intracerebral hemorrhage from ages 45-54,.(Ekker et al., 2018; Ekker et al., 2019; Feng et al., 2009; George et al., 2017; Tong et al., 2016). The review of current literature revealed varying definitions of age for young stroke, the goal of this review is to systematically assess the variability in outcomes reported for young adults with stroke across all age groups.

Current evidence reveals numerous risk factors among young adults including hypertension, hypercholesterolemia, diabetes mellitus, smoking, and obesity have increased in prevalence (Ekker et al., 2018). However, there are a myriad of unique risk factors that are specific to a young adult population that differ from the standard modifiable vascular risk factors among older patients (Smajlović, 2015). This review will highlight the risk factors present among young adults with stroke (YAS) and future work can focus on association with stroke for

both the clinical and acute care environment as well as public health sphere for prevention and education to both clinicians and patients.

The burden of stroke on young adults is of special concern and interest as they are our working-age population. This population of young patients is commonly starting families, navigating demanding careers, and participating in social activities daily, all of which may have long term impact. This can be attributed to the lack of administration and accessibility of post-acute rehabilitation services and difference between their needs and services offered (Morris, 2011).

The literature supports 10 years post-stroke, 1 in 8 YAS have poor functional outcomes and 14 years post stroke, 1 in 5 YAS are not able to live independently (Synhaeve et al., 2016). These outcomes can be attributed to the common long-term consequences of YAS including pain, cognitive impairments, mental illness and in the inability to return to work (Varona, 2011). Evidence shows needs of 18-55 year old are frequently not met including addressing psychological needs in terms of anxiety and depression, structured support such as resources for return to work, and invisible deficits such as fatigue and self-efficacy (Chang et al., 2020; Shipley et al., 2020). YAS have three-time higher depressive symptoms and two-time higher prevalence of anxiety than healthy counterparts (Ekker et al., 2018). In fact, stroke in young adults have a three to six times greater risk of suicidal attempts (Ekker et al., 2018). Approximately 50% of individuals had depression and 66% had anxiety (Teasell et al., 2000) and post-stroke depression ranges 28-46% (Singhal et al., 2013). Source of anxiety came from return to work (48%) then concerns over recovery (25%) and childcare (17% of those with children) (Teasell et al., 2000).

While the number of young adults suffering from stroke is substantial, utilizing the Trial of Org 10172 in Acute Stroke Treatment. (TOAST) criteria, etiology remains unknown in 25-50% of these patients (van Alebeek et al., 2018; Yahya et al., 2020). The functional outcomes post-stroke for young adults can range from mild deficits to debilitating cognitive and physical impairments that require constant caregiver support (Jin et al., 2018). These individuals with young stroke need appropriate, affordable long-term healthcare services. Lack of appropriate rehabilitation can result in larger dependency costs and the economic benefits of rehabilitation specific for working age adults can have profound effects for functional outcomes but also have major economic benefits and even offset costs of dependency. One study with 31 patients in the NHS system showed positive effects in lowering overall care costs for patients who engaged in rehab for a median length of 59 days; the total savings in care costs for the 31 patients were close to 2 million dollars in the course of a year (O'Connor et al., 2011). Studies have shown that the current recommendations for treatment of young and old patients with stroke are similar, however the optimal management of YAS is unknown as the continuation of care for individuals with stroke is tailored towards the older population.(Ekker et al., 2019) This need for unique tailored care to YAS is a gap in knowledge and research regarding these individuals, a gap we intend to explore.

The objective of this scoping review is to synthetize the literature on epidemiological factors, clinical characteristics, outcomes, and utilization of post-acute care services among young adults with stroke.

Methods:

Design:

A scoping review of the literature was performed in order to determine the gaps in knowledge and available information regarding age associated presentation, epidemiology, risk factors, and health service utilization among young adults with stroke. This review will be registered in Open Science Framework. Scoping reviews are an approach to data and information extraction/synthesis in order to explore novel research questions by including all available existing research. This systematic scoping review followed the guidelines as provided by The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).(Page et al., 2021)

Search Strategy:

Working with an Emory University medical librarian, a list of key search terms was compiled. This was done by reviewing articles and highlighting the key terms that were present in each article. The search strategy was divided into key words to be included in the titles of the articles and key words within the abstract. The main key search terms that were included consisted of "Stroke", "Strokes", "Young Stroke", "Younger Stroke", "Young men/women", "Younger Patient", and "Cerebrovascular Accident". Once the list of key terms was solidified the medical librarian conducted a search in five different information sources which included PubMed, Embase, CINAHL, PsychINFO, and Web of Science. The following is the search terms, Young[ti] or younger[ti] or age[ti] or midlife[ti] or young stroke[tiab] or younger stroke[tiab] or young patient[tiab] or younger patient[tiab] or young patients[tiab] or younger patients[tiab] or young population[ti] or young populations[tiab] or younger populations[tiab] or younger populations[tiab] or young women[tiab] or younger women[tiab] or young men[tiab] or

younger men[tiab] or young adult[tiab] or young adults[tiab] or younger adult[tiab] or younger adults[tiab] or young stroke[tiab] or young strokes[tiab] or younger stroke[tiab] or younger strokes[tiab] or young age[tiab] or younger age[tiab] or young ages[tiab] or younger ages[tiab].

Screening:

Using Covidence, an online data management software, ten reviewers independently screened abstracts for inclusion and exclusion criteria; each abstract was voted upon by two independent reviewers to limit bias, with a third independent reviewer providing conflict resolution. An article was included if it contained epidemiology for young stroke, risk factors for young stroke, post stroke outcomes and symptoms, and post-acute healthcare service utilization. The exclusion criteria were Studies with non-human populations, reviews, conference abstracts, case reports, textbook chapters, editorials, studies that solely studied TIA or grouped stroke and TIA together, articles with data collected prior to 2003 to ensure data aligned with the 200, participants younger than 18 or older than 65, no age range defined, surgical and pharmacological interventions, sample size less than or equal to 5, duplicates, and prevention studies were excluded during both title and abstract screening as well as full text screening. For studies with no age range defined, attempts were made to contact corresponding authors to determine eligibility in the study. Of the original 11,858 entries received from the initial search, 5,097 were excluded as duplicates, 3,491 studies were excluded during title and abstract screening leaving 2,347 articles to be considered in the full-text review. Of the articles considered for full-text review 2118 have been excluded, while 187 articles have been included for final data extraction. A summary of this data can be found in Figure 1 as well as the major reasons for exclusion.

Data Extraction:

Using Covidence, a data extraction template was generated after ample discussion and multiple edits and reviews. Articles that included any variables of interest such as epidemiology, risk factors, post-stroke outcomes and post-acute healthcare service utilization across diverse demographics, age groups (18-65), stroke subtypes and temporal trends were extracted. Ten reviewers participated in data extraction, with each article extracted by two independent reviewers and the primary investigatory (Joseph) acting as the final review of data for accuracy of data synthesis. Any discrepancies in data extraction/synthesis were resolved through group consensus of no less than 3 individuals.

Variables:

We extracted the following data from each study, title, author, publication year, country, data set source, study design, start and end data, type of stroke included, National Institutes of Health Stroke Scale (NIHSS) stroke severity, demographics of study samples including age, race marital status, education, as well as, first ever stroke/recurrent stroke, setting, incidence/prevalence, racial disparities, hospitalization rates, mortality, length of stay, risk factors, etiology, physical functional outcomes, cognitive outcomes (memory, attention, awareness), psychological outcomes (anxiety, depression), psychosocial outcomes (marital stress, fatigue, fears, child care, environment), return to work, post-acute care discharge destination, type of rehab received and outcomes following rehab (post acute care services), attitudes toward post stroke rehab care, cost (acute care), costs (rehab), costs (any indirect costs). NIHSS is was used to assess stroke severity due to its proven validity, standardization across many studies, and comprehensiveness assessing stroke across multiple facets including motor function, cognition, speech, vision, and level of consciousness; scores ranged from 0 to 42, very

severe > 25, severe 15-24, mild to moderately severe 5-14, mild 1-5 (Brott et al., 1989; Lyden et al., 1999). Modified Rankin Score (mRS) a measure of disability was used to assess physical functional outcomes among YAS, this measure has proven validity and reliability for clinicians and researchers; a score ≤2 indicates a favorable outcome with little disability, while a score >2 indicates an unfavorable outcome and YAS will have disability.(Banks & Marotta, 2007). Cognitive impairment was assessed through multiple variables including aphasia, Montreal Cognitive Assessment (MoCA) Global Cognitive Function and Glasgow Coma Scale (GCS). The MoCA has both high sensitivity and specificity for detecting cognitive impairment across attention, memory, visuospatial, language, and orientation; a MoCA score <26 indicates cognitive impairment (Nasreddine et al., 2005). The Glasgow Coma Scale (GCS) measures consciousness through eye, motor and verbal response and has proven inter-test reliability, and validity across numerous clinical settings and thus proved to be a valuable measure to determine cognitive impairment among YAS; a GCS <11 indicates cognitive impairment (Fischer et al., 2010).

Results:

Studies Summary:

Of the 11,858 studies initially identified, 187 were included in the final review after data extraction. The PRISMA Flowchart created by Covidence lists the steps at which each article was excluded (Figure 1). The most common reasons for exclusion during full-eligibility assessment were studied including individuals outside the age range of 18-65 (n=774 studies), case reports, newsletters, editorials, conference abstracts, correction, textbook chapters, reviews (n=729 studies), and data obtained before 2003 (n=455 studies).

Supplemental Table 1, provides details on all articles used for this review including the country where the study was conducted, sample size, setting, and study design. The majority of studies took place in the United States (22%), China (18%) and India (11%); Figure 2 highlights the top 10 Countries. Additionally, the majority of studies were cohort studies (n=60), and cross-sectional studies (n=52), as well as included case-control (n=33), qualitative (n=13), randomized control trials (n=3), case-series (n=2) and not reported (n=21) studies (Figure 3). Furthermore, the relationship between the year studies were published and the number of published studies exponentially increase over time from 2004 to 2021 (Figure 4).

Demographics:

Table 1 describes the overall demographics of the YAS across studies. Sample size included in this review was 1,093,366 YAS, with an age range between 18-65, and a mean age of 37 years old for studies that reported mean age (n=127). The median age is 45 years (IQR 41-53 yrs.), and the range of medians reported was 38-59 years for studies that reported median age (n=35). For studies that stratified by gender, the average number of females was 52% of the overall sample, and 48% were male (n=169).

However, there was inconsistency in how young adults we defined across studies, with 43% of studies defined young adults between 18-50, 26% between 18-45, and 12% between 30-65 years. The setting of studies varied, with 53% taking place in single-site hospitals, 20% in multi-site hospital, 16% in in-patient or outpatient rehabilitation centers, 5% in participant homes, and 11% not reporting or other.

Stroke types varied less across studies with 144 (77%) studies including ischemic stroke participants, 50 (27%) studies included hemorrhagic stroke (intracerebral hemorrhage and subarachnoid hemorrhage), and only 17 (9%) studies included cryptogenic stoke.

Furthermore, 28% of studies included only individuals with first ever stroke, 19% included individuals with both a first stroke or recurrent stroke while 54% did not report whether it was a first ever stroke or both. The mean NIHSS was 6.6 (n=12) and the median was 3 (IQR 1-4, range 3-11) (n=27). The average mortality among YAS was 1.4% (n=19). The median length of stay (LOS) in acute care was 7 days (n=11) and the mean LOS was 10 days (n=7).

Incidence:

Temporal trends of incidence were minimally reported, with only 2 studies showing trends. One study showed a consistent linear increase in hospitalization rates for acute ischemic stroke (AIS), among 35-64 years, from 2006-2007 to 2016-2017 increasing from 71 to 125 hospitalizations per 100,000 respectively (Figure 5).(Tong et al., 2020) Additionally, another study showed changes in hospitalization from 2004 to 2014, among 18–65 years. AIS decreased from 60 to 57 hospitalizations per 100,000 ($p=0.055$), subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH) increased from 62 to 77 ($p< 0.0001$) and 52 to 67 ($p < 0.0001$) hospitalizations per 100,000 respectively (Figure 6).(Sipila et al., 2018) Fourteen studies summarize incidence of stroke across racial groups Table 2. The total cases of YAS across these

studies were 2,488,929, 61% were white, 23% Black, 10% Hispanic, 5% other, 1% Asian/Pacific Islander, <1% Native.

Risk Factors:

Risk factors were reported across 51 studies, the total sample size of all studies was 15,405 YAS (Table 3). The risk factors summarized were Hypertension, Smoking, Diabetes Mellitus, Heart Disease/ CVD, Alcohol Consumption, Hypercholesterolemia, Hyperlipidemia / dyslipidemia, Patent foramen ovale (PFO), Patent foramen ovale and atrial septal aneurysm (PFO+ASA), Atrial Fibrillation, Migraine (with and without Aura), Hyperhomocysteinaemia, Family History of Stroke, Prior Stroke or TIA, Illicit Drug Use (Includes Marijuana), Oral Contraceptives, and Obesity. Among all these studies the top 5 risk factors were 51% of YAS had hypercholesterolemia smokers (n=6), 45% were smokers (n=42), 40% had hypertension (n=42), 29% had a family history of Stroke or TIA (n=7), and 28.2% had hyperhomocysteinaemia (n=4). Risk factors with the smallest number of studies citing them as risk factor include PFO + ASA, hyperhomocysteinaemia, oral contraceptives, hypercholesterolemia, PFO, and illicit drug use.

Post-Acute Care Outcomes:

Physical function outcomes were summarized across 21 studies using mRS. The average mRS score was 1 (n=9). 58% of YAS had a mRS between 0-2 (n=13), while 42% had a mRS >2 (n=12) (Table 4). Cognitive impairment was assessed across 18 studies. Outcome measures used to assess impairment was the presence of aphasia, MoCA Global Cognitive Function scores and GCS scores. On average 12% of YAS across 18 studies had cognitive impairment post-acute care. Psychological outcomes were assessed across 14 studies (Table 5). On average 40% of YAS (n=14) had depression and 37% of YAS (n=7) had anxiety (Table 6). In terms of discharge

destination, there was minimal comprehensive data concerning the location in which YAS went post-acute care. 56% were discharged home (n=13), 8% were discharged to home health (n=2), 13% in-patient rehabilitation (n=9), 23% skilled nursing facility (SNF) (n=4), 3% outpatient rehabilitation (n=3), 1% nursing home (n=5), and 5% had died or had unknow discharge destination (Table 7, Figure 7). Lastly, return to work was investigated in 19 articles. 63% of YAS returned to full time work (n=19), 18% (n=4) of YAS returned to partial of adjusted work, 42% (n=18) of YAS did not return to work (Table 8).

Discussion:

The burden of young adult stroke is especially of concern and interest because of a working age population. The functional outcomes post stroke for young adults can range from mild effects to cognitive and physical impairments that increase the overall burden of disease. Sequelae included motor deficits, cognitive dysfunction, adverse mental health symptoms, and fatigue. There is a gap of information in stroke care in hospitals and following hospital discharges among young adults. The literature underscores a lack of adequate, appropriate and tailored post-acute care health services , where young stroke survivors feel they are “being left in the trench”(Martinsen et al., 2015). There is a significant gap in the literature on the psychosocial outcomes and unique invisible deficit concerning YAS. Mild stroke often presents with non-disabling and rapidly improving symptoms (Roberts et al., 2020). Therefore, these individuals are less likely to receive acute diagnostic tests and treatments along with long term rehabilitation(Roberts et al., 2020). Young adults often experience mild strokes, therefore fall into this category (Lutski et al., 2017). YAS have unmet psychosocial needs and fearful and isolated outlooks on life, 44% of YAS have at least one unmet psychosocial need, and individuals with an mRS >2 have an even greater unmet need. (Keating et al., 2021; D. M. Leahy

et al., 2016). Stroke not only plays a physical and mental role in recovery, but the financial burden can have the greatest effect on a working age population. Therefore, understanding the financial stress associated with acute and post-acute care allows for a nuanced approach to this research question that goes beyond physical and mental outcomes. In the united states a majority of individuals have private insurance (42%), and of these individuals a majority receive health insurance through their employer (Jin et al., 2018). Thus, not returning to work, potentially loosing access to employer sponsored insurance coupled with post-acute care health costs can cause a severe financial burden on YAS.

Recommendations for future works include greater stratification of YAS across racial/ethnic groups. As previously mentioned, there are clear associations between racial disparities and stroke, however there is little research looking at the association between YAS and race. Furthermore, for example, African Americans adults younger than 65 years of age are more likely to have longer hospitalizations, higher mortality and morbidity, greater incidence of severe stroke, four times more likely to have an intracerebral hemorrhage, and less likely to be discharged home in comparison to their Caucasian counterparts (Boan et al., 2014; Feng et al., 2009). Consequently, this will incur greater health care costs for African Americans, 23-36 million per year in comparison to their Caucasian counterparts (Boan et al., 2014; Feng et al., 2009). Additionally, there was a lack of reporting of discharge destination. This is imperative to understand the severity of stroke on Young Adults and can help better understand the journey one takes through their stroke beyond acute care to then create the necessary services to meet their needs. A strength of our study is the incorporation of many diverse regions to highlight geographic variations among YAS. A major difference our study hopes to add to the literature is understanding the utilization of rehabilitation services among YAS. This has major implications

in future educational and informational clinical guidelines in the treatment of YAS and can play a role in decreasing the burden of disease. Some limitations of this study are that the information presented in a scoping review is only as strong as the information presented in each study and thus with each study careful and thoughtful reasoning of individual limitations needs to be assessed. In conclusion, this study is important to understanding a working-age population and the burden of stroke plays in their daily lives. This study will hopefully act as a catalyst for greater research in the investigation for decreasing the burden of illness young stroke presents.

Conclusion:

Preliminary results uncover the need for greater insight into the effect of stroke among this population. The results of this study highlight the needs and deficits in care among young stroke survivors, individuals who care for families, active members of the workforce, and significantly affected in daily life. Unique risk factors, increasing incidence and prevalence, racial disparities, unknown etiologies, as well as short and long term sequala specifically underlying invisible are all factors contributing to the importance of understanding stroke through the lens of young adults. Additionally, greater efforts need to be made into overcoming the barriers to rehabilitation and increasing accessibility to all post-acute healthcare services. Ultimately future studies in this area will work towards a potential mixed methods studies addressing specific survivors concerns with data from single and multi-site stroke data with long term working to address these concerns with effective multi-faceted interventions .

Tables and Figures:

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart

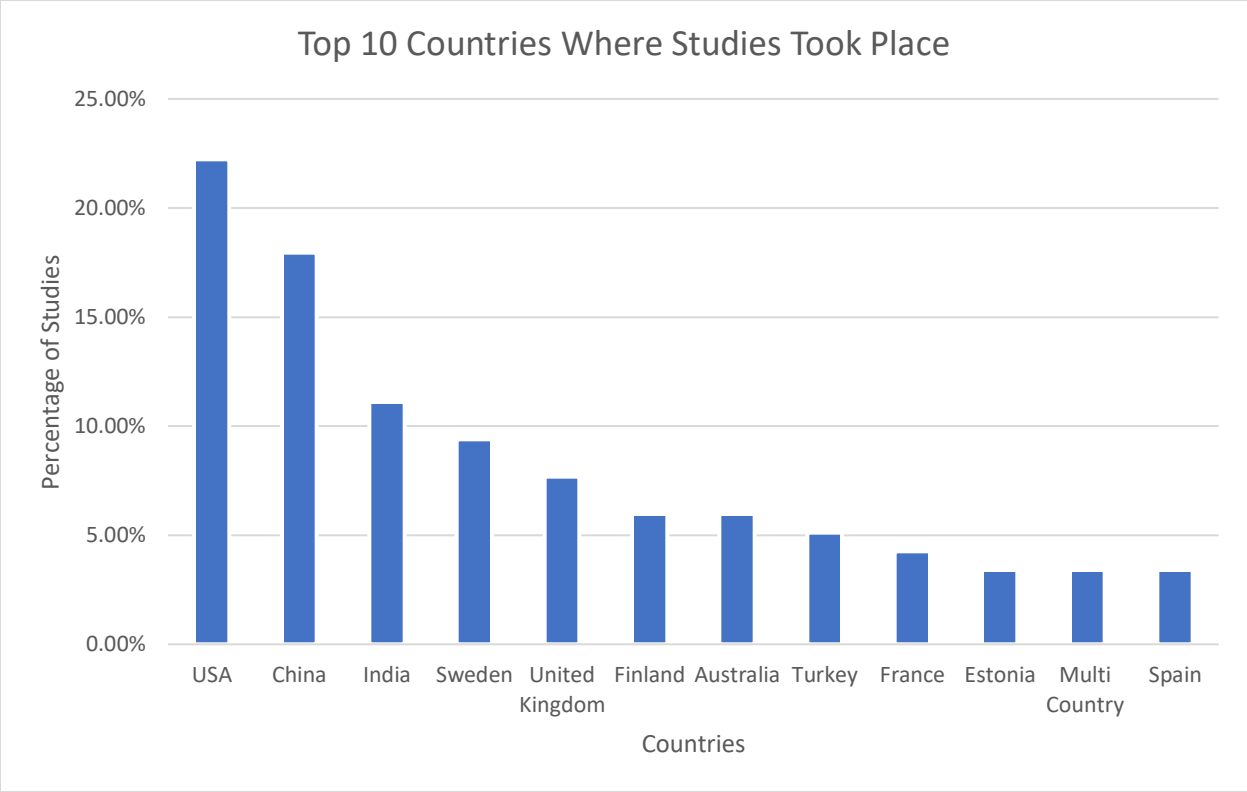

Figure 2: Countries of Where Studies Took Place (Top 10)

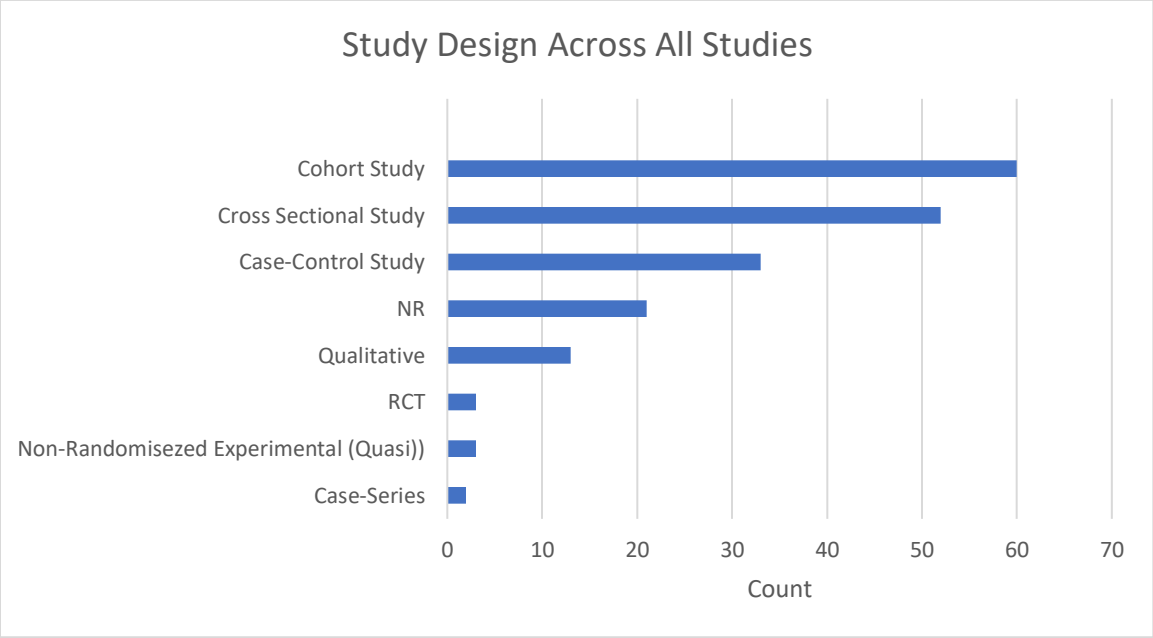

Figure 3: Study Design Across all Studies

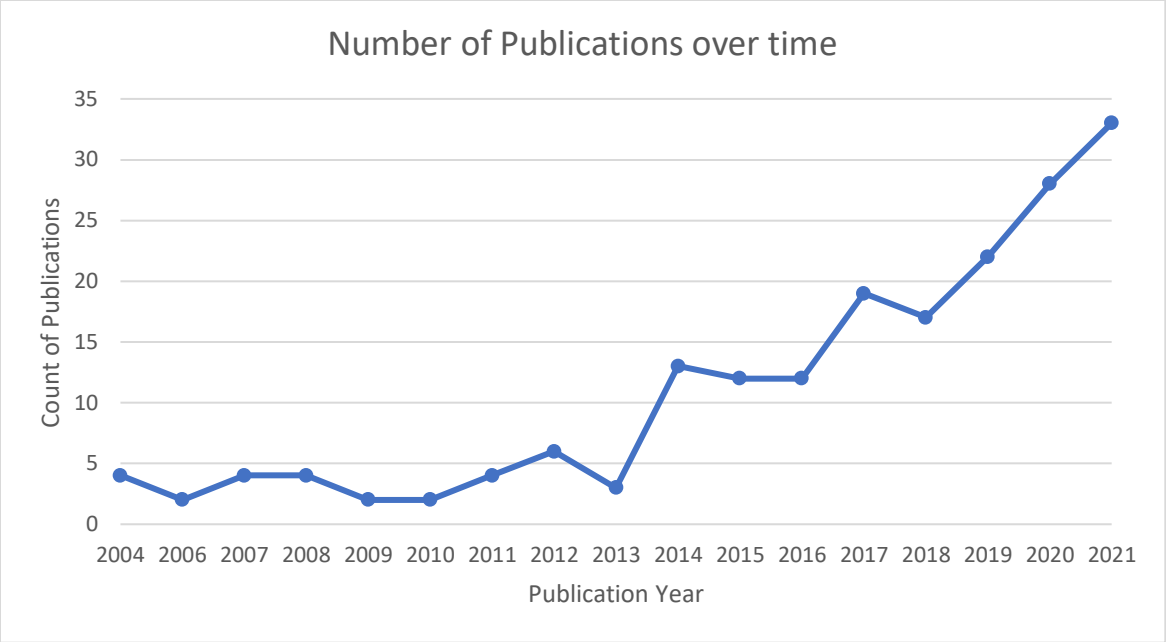

Figure 4: Number of Studies per year from 2004-2021

Table 1: Demographic Table

Variable	Value
Total Sample Size of YAS	1093366
Mean Age (n=127)	37
Median Age (n=35) (IQR, Range)	45 (41-53, 38-59)
Females (%) (n=169)	52%
Age Range	18-65
Ange Range Stratification:	
18-50 yrs (%)	43%
18-45 yrs (%)	26%
30-65 yrs (%)	12%
Setting of Studies: (% of studies)	
Single-site hospitals	53%
Multi-Site Hospitals	20%
In-Patient/Out-Patient Rehabilitation	16%
Home	5%
NR	11%
Stroke Subtype (% of studies)	
Ischemic	77%
Hemorrhagic Stroke	27%
Cryptogenic Stroke	9%
First Ever Stroke (% of studies)	28%
Both First and Recurrent Strokes (% of studies)	19

Mean NIHSS (n=12)	6.6
Median NIHSS (n=27) (IQR, Range)	3 (IQR 1-4, range 3-11)
Average Mortality (%) (n=19)	1.40%
Median Length of Stay in Acute Care (n=11) (days)	7
Mean Length of Stay in Acute Care (n=7) (days)	10

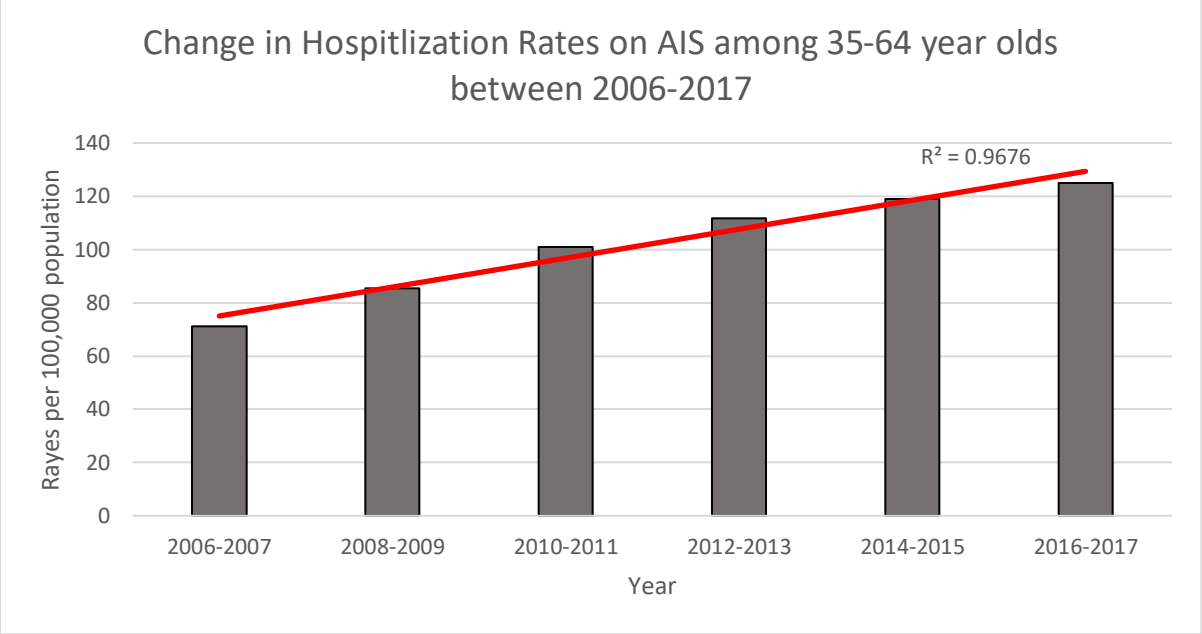

Figure 5: Change in hospitalization Rates for Acute Ischemic Stroke (AIS) among 35-64 year old between 2066-2017, R^2=0.97, rates per 100,000(Tong et al., 2020)

Table 2: Incidence of YAS Across Racial Groups

Table of Cases of YAS Across Race							
Source	Total	White	Black	Hispanic	Other	Asian/Pacific Islander	Native
(Tong et al., 2020)	1,509,203	878,356	387,865	146,393	96,589		
(Patel et al., 2021)	191,568	104,485	57,382	23,310		5,158	1,233
(Wolff et al., 2014)	159	158			1		
(Hassan & Yarube, 2018)	47		47				
(Rhudy et al., 2020)	30	26	2	1		1	
(Kuybu et al., 2020)	784,925	537,365	124,930	84,035	22,530	11,155	4,910
(Leung & Caplan, 2016)	141	107			34		
(Nakagawa et al., 2017)	427	74				353	
(Dardick et al., 2021)	204	31	173				
(Jones et al., 2020)	810	296	350	164			
(Keating et al., 2021)	165	148			17		
(Tsivgoulis et al., 2014)	1,134	551	271			312	
(Harris Walker et al., 2021)	10	6	3		1		
(Miller et al., 2018)	106	31	22	30	23		
Grand Total	2,488,929	1,521,634	571,045	253,933	119,195	16,979	6,143
Percent		**61.1%**	**22.9%**	**10.2%**	**4.8%**	**0.7%**	**0.2%**

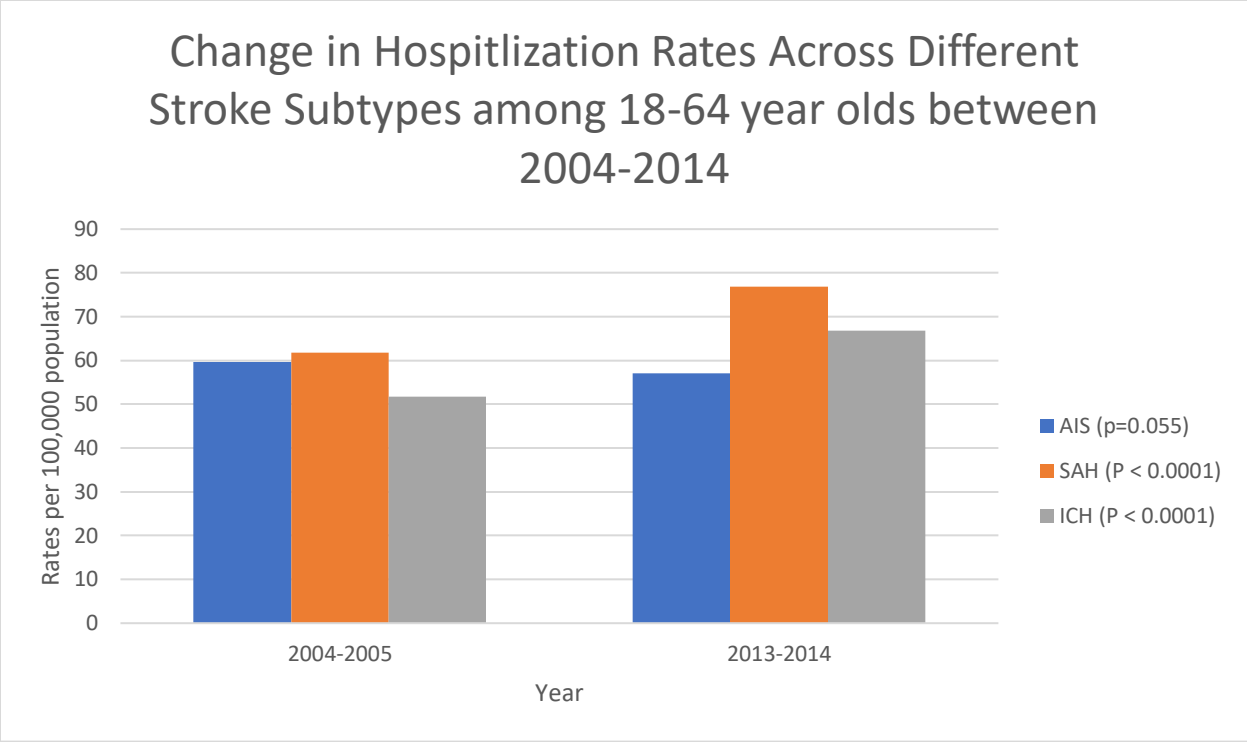

Figure 6: Change in Hospitalization Rates Across Stroke Subtypes among 18-64 years between 2004-2014(Sipila et al., 2018)

Table 3: Risk Factors for YAS

Risk Factor	Number of Studies	Percent of YAS
Hypercholesterolemia (%)	6	50.8
Smoking (%)	42	44.8
Hypertension (%)	42	39.5
Family History of Stroke (%)	7	28.7
Hyperhomocysteinaemia (%)	4	28.2
Alcohol Consumption (%)	22	27.9
Hyperlipidemia / dyslipidemia (%)	26	27.4
Migraine (with and without Aura) (%)	12	18.5
Obesity (%)	9	18.1
Prior Stroke or TIA (%)	9	15.3
Diabetes Mellitus (%)	44	14.3
PFO (%)	6	13.8
Heart Disease/ CVD (%)	25	11.0
Atrial Fibrillation %	18	10.3
PFO + ASA (%)	2	9.1

Illicit Drug Use (Includes Marijuana) (%)	6	6.9
Oral Contraceptives (%)	4	3.6

Table 4: Physical Function Outcomes Described through Modified Rankin Score (mRS)

Source	Sum of mRS 0-2	Sum of mRS >2	Average mRS
(Bonner et al., 2016)			3
(Von Sarnowski et al., 2017)			2
(Pinter et al., 2019)			1
(Indira Priya et al., 2019)			2
(Westerlind et al., 2017)	51%	49%	1.3
(Tsivgoulis et al., 2014)	49%		
(Priya et al., 2021)	29%	71%	
(Marto et al., 2018)	76%	24%	
(Törnbom et al., 2019)	55%	45%	
(Tan et al., 2014)	32%	65%	
(Balci et al., 2011)			2.4
(Zhang et al., 2019)	67%	33%	
(Cejas et al., 2019)			1.59
(Aguilera-Pena et al., 2021)	97%	2%	
(Saban et al., 2019)	50%	50%	2.9
(Olibamoyo et al., 2019)			
(Rutkowski et al., 2021)			2.24
(Schneider et al., 2021)	55%	44%	
(Cain et al., 2021)	72%	28%	
(Xu et al., 2021)	74%	26%	
(Zhou et al., 2018)	62%	38%	
Weighted Average	58%	42%	0.88

Table 5: Cognitive Outcomes Among YAS

Source	Average YAS with Impaired Cognitive Status (INCLUDING Aphasia, MoCA Global Cognitive Function <26, Glasgow Coma Scale <11)
(Saban et al., 2019)	10.0%
(Zhang et al., 2019)	33.3%
(Indira Priya et al., 2019)	78.0%

(MacIntosh et al., 2021)	5.8%
(Bonner et al., 2016)	24.1%
(Huang et al., 2015)	39.4%
(Cejas et al., 2019)	6.4%
(Hassan & Yarube, 2018)	78.7%
(Pinter et al., 2019)	42.1%
(Hackett et al., 2012)	23.2%
(Geng et al., 2019)	4.8%
(Chraa et al., 2014)	34.4%
(Baghel et al., 2020)	58.0%
(Glozier et al., 2017)	16.8%
(Quinn et al., 2014)	25.0%
(Kauranen et al., 2015)	56.5%
(Westerlind et al., 2019)	40.7%
(O'Connor et al., 2011)	17.1%
Weighted Average	**12.1%**

Table 6: Psychological Outcomes of Depression and Anxiety Among YAS

Article	Depression (%)	Anxiety (%)
(Schneider et al., 2021)	67.3	69.6
(Yu et al., 2016)	23.1	
(Liang et al., 2021)	14.2	24.7
(Bonner et al., 2016)	41.8	55.3
(Si Larbi et al., 2021)	7.3	
(Maaijwee et al., 2016)	19.5	23.1
(Priya et al., 2021)	28.7	16.0
(Priya et al., 2021)	56.0	
(Olibamoyo et al., 2019)	42.9	
(Hackett et al., 2012)	20.7	
(Glozier et al., 2017)	13.9	23.1
(Amaricai & Poenaru, 2016)	22.2	
(Lannin et al., 2017)	48.0	48.0
(Opoku et al., 2020)	100.0	
Weighted Average	**39.8**	**37.2**

Table 7: Discharge Destination Among YAS

Source	Home (%)	Home-Health (%)	In-Patient Rehab (%)	Skilled Nursing Facility (%)	Out-Patient Rehab %	Nursing Home/ Aged Care Facility (%)	Other (Died, Unknown) (%)
(Opoku et al., 2020)	11.1%				53.7%	5.6%	
(Wolfenden & Grace, 2015)			40.0%		40.0%		
(Prefasi et al., 2013)	83.4%		14.0%			2.5%	
(Westerlind et al., 2019)	88.1%		8.9%				2.1%
(Jones et al., 2020)	52.7%						
(Skolarus et al., 2012)	77.3%		14.8%	8.0%			
(Lannin et al., 2017)	52.3%		25.0%			0.5%	
(Saban et al., 2019)	30.0%		70.0%				
(Jin et al., 2018)	65.6%	11.0%	2.3%	12.5%	2.3%		8.5%
(Rhudy et al., 2020)	66.7%		13.3%	16.7%			3.3%
(O'Connor et al., 2011)	80.0%					17.1%	2.9%
(Walters et al., 2020)	57.5%		39.1%			0.7%	
(Tong et al., 2020)	54.4%						
(Patel et al., 2021)	61.3%	7.5%		26.1%			33.6%
Weighted Average	**55.69%**	**7.72%**	**13.43%**	**22.89%**	**2.54%**	**0.66%**	**4.45%**

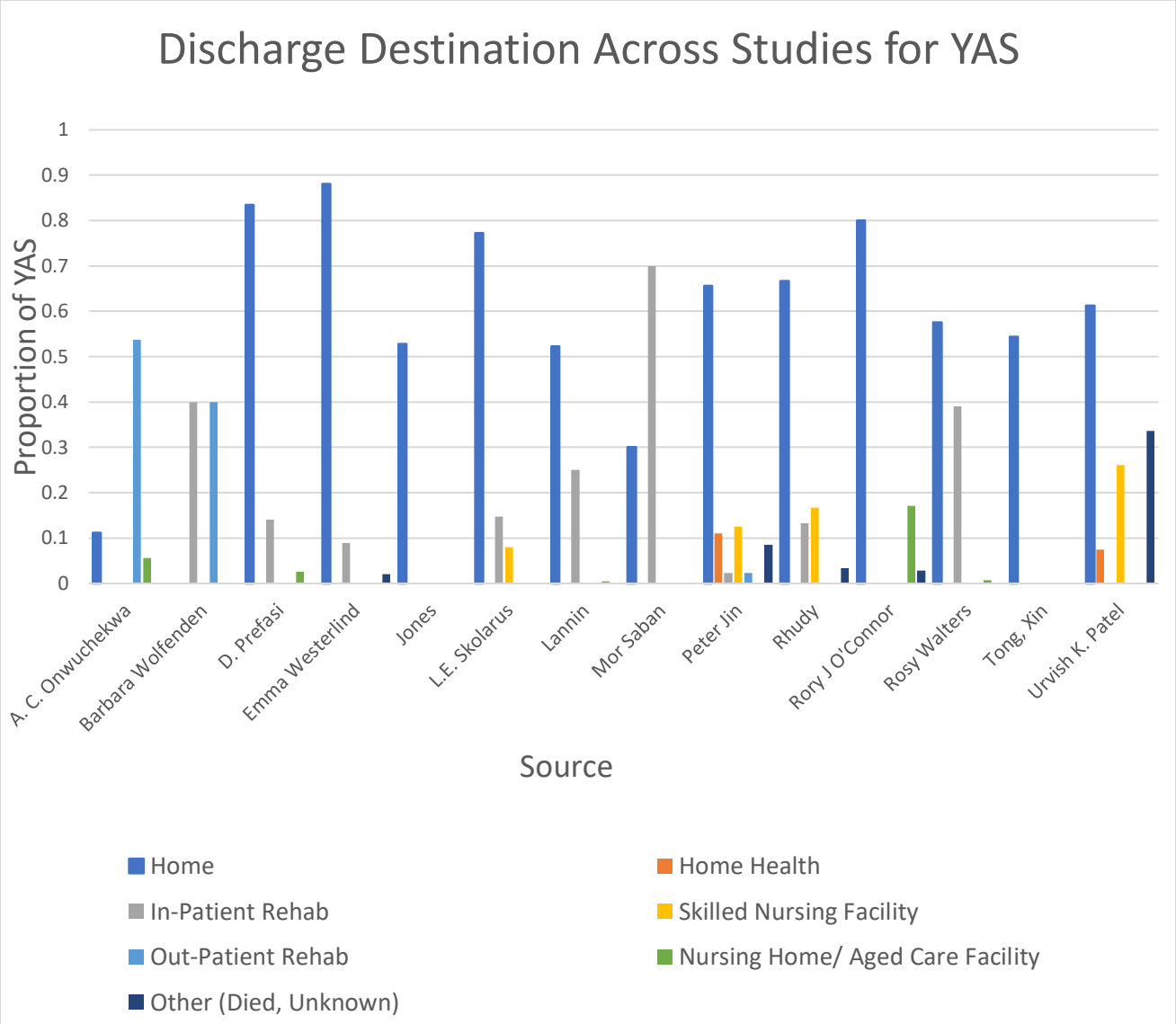

Figure 7: Discharge Destination Among YAS

Table 8: Return to Work Among YAS

Article	Full Time RTW %	Returned to Partial / Adjusted Work %	Did Not RTW %	Mean Time to RTW (Months)
(Bonner et al., 2016)	52%		48%	3.9
(Wolfenden & Grace, 2015)	100%		0%	7.4
(Grenthe Olsson & Sunnerhagen, 2007)	6%	16%	76%	
(Björkdahl & Sunnerhagen, 2007)	7%		93%	
(Glader et al., 2017)	74%		47%	12
(Westerlind et al., 2017)	140%		60%	
(Glozier et al., 2017)	75%		25%	
(Jarvis et al., 2019)	23%		77%	
(Shipley et al., 2020)	71%		29%	
(Quinn et al., 2014)	6%		19%	
(Törnbom et al., 2019)	73%	9%	18%	
(Hackett et al., 2012)	45%	30%	25%	
(Manning et al., 2021)	15%		85%	
(Muller et al., 2014)	8%			
(Kersten et al., 2004)	11%	9%	53%	
(Walters et al., 2020)	61%		39%	
(Rutkowski et al., 2021)	67%		33%	
(Anderson & Whitfield, 2013)	22%		22%	
(Yu et al., 2016)	73		27%	
Weighted Average	63%	18%	42%	12

Supplemental Table 1: All Studies Included in Review (Includes Country, Study Design, and Total Sample Size)

Title	Country in which the study conducted	Study Design (P/R)	Study design	Total sample size
(Jaffre et al., 2017)	NR	Retrospective/Observational	Cross Sectional Study	164
(Jaffre et al., 2015)	NR	Retrospective/Observational	Cross Sectional Study	400
(Onwuchekwa et al., 2009)	Nigeria	Retrospective/Observational	descriptive	54
(Dahshan et al., 2019)	Egypt	Prospective	Case-Control Study	33
(Gürdal et al., 2018)	Turkey	Prospective	Cohort Study	40
(Holloway et al., 2021)	United Kingdom	Retrospective/Observational	Qualitative	103
(Alaszewski & Wilkinson, 2015)	United Kingdom	Prospective	Cohort Study	43
(Alenljung et al., 2019)	Sweden	Prospective	Cohort Study	10
(Pezzini et al., 2004)	Italy	Prospective	Case-Control Study	124
(Rodríguez-Sanz et al., 2015)	NR	Prospective	Cross Sectional Study	255
(Lasek-Bal & Gąsior, 2016)	Poland	Prospective	NR	611
(Liu et al., 2018)	USA	Retrospective/Observational	Cohort Study	175
(Aigner et al., 2017)	Germany	Retrospective/Observational	Case-Control Study	2125
(Bonner et al., 2016)	India	Retrospective/Observational	Cross Sectional Study	141
(Wolfenden & Grace, 2015)	Australia	Retrospective/Observational	Qualitative	5
(Grenthe Olsson & Sunnerhagen, 2007)	Sweden	Prospective	NR	50
(Von Sarnowski et al., 2017)	Europe	Prospective	Cross Sectional Study	2101

(Björkdahl & Sunnerhagen, 2007)	Sweden	Prospective	RCT	58
(Gollion et al., 2021)	France	Retrospective/Observational	Cross Sectional Study	339
(Chatzikonstantinou et al., 2012)	Germany	Retrospective/Observational	Cohort Study	104
(Geng et al., 2019)	China	Prospective	NR	228
(Shi et al., 2008)	China	Retrospective/Observational	Case-Control Study	97
(Lu et al., 2016)	China	Retrospective/Observational	Cross Sectional Study	84
(Pinter et al., 2019)	Austria	Prospective	NR	114
(Prefasi et al., 2013)	Spain	Retrospective/Observational	Cross Sectional Study	157
(John et al., 2020)	India	Prospective	Case-Control Study	50
(Šaňák et al., 2015)	Czech Republic	Prospective	Cohort Study	98
(Dash et al., 2014)	India	Retrospective/Observational	Cohort Study	440
(Desai et al., 2020)	USA	Retrospective/Observational	Cohort Study	34857
(Ao et al., 2015)	China	Prospective	Case-Control Study	11
(Dimitrov et al., 2020)	Bulgaria	Prospective	Cohort Study	63
(Priya et al., 2021)	India	Retrospective/Observational	Cross Sectional Study	150
(Dorothy M. Leahy et al., 2016)	Ireland	Retrospective/Observational	Qualitative	12
(Glader et al., 2017)	Sweden	Retrospective/Observational	Cross Sectional Study	2539
(Amaricai & Poenaru, 2016)	Romania	Prospective	Cross Sectional Study	72
(Miller et al., 2018)	USA	Retrospective/Observational	Cross Sectional Study	130
(Westerlind et al., 2017)	Sweden	Retrospective/Observational	Cross Sectional Study	211

(Westerlind et al., 2019)	Sweden	Retrospective/Observational	Cohort Study	145
(Elgh & Hu, 2019)	Sweden	Prospective	Cohort Study	425
(Elgh & Hu, 2020)	Sweden	Prospective	Cohort Study	38
(Li et al., 2017)	China	Retrospective/Observational	Cross Sectional Study	1,395
(Chang et al., 2020)	Taiwan	Retrospective/Observational	Qualitative	25
(Harris Walker et al., 2021)	USA	Prospective	NR	10
(Gans et al., 2021)	USA	Retrospective/Observational	Cohort Study	121
(Magwood et al., 2017)	USA	Retrospective/Observational	Cohort Study	125
(Geneme et al., 2019)	USA	Prospective	Non-Randomiseze d Experimental (Quasi))	21
(Gehefer et al., 2019)	USA	Retrospective/Observational	NR	3900
(Tsivgoulis et al., 2014)	Multi Country	Retrospective/Observational	Cross Sectional Study	1134
(Glozier et al., 2017)	Australia	Prospective	Cohort Study	368
(Wang et al., 2015)	USA	Retrospective/Observational	Cohort Study	40082
(Gündoğdu et al., 2017)	Turkey	Prospective	Cohort Study	54
(Byeon & Koh, 2015)	Korea	Retrospective/Observational	Cross Sectional Study	33
(Jarvis et al., 2019)	United Kingdom	Prospective	Cohort Study	46
(Hassan et al., 2020)	Iraq	Retrospective/Observational	Cross Sectional Study	50
(Ying et al., 2013)	China	Retrospective/Observational	Case-Control Study	186
(Huang et al., 2019)	China	Retrospective/Observational	Cohort Study	961
(Huimin et al., 2018)	China	Retrospective/Observational	Cross Sectional Study	400

(Ali & Abdullah, 2008)	Iraq	Retrospective/Observational	Case-Control Study	50
(Imran et al., 2015)	Indonesia	Prospective	Case-Control Study	107
(Indira Priya et al., 2019)	India	Retrospective/Observational	Cross Sectional Study	150
(Cojocaru et al., 2007)	Romania	Retrospective/Observational	Case-Control Study	34
(Cojocaru et al., 2008)	Romania	Prospective	Cohort Study	46
(Iqbal et al., 2017)	Pakistan	Retrospective/Observational	Cohort Study	200
(Isordia-Salas et al., 2019)	Mexico	Retrospective/Observational	Case-Control Study	244
(Delilović-Vranić et al., 2011)	Bosnia	Prospective	Cohort Study	132
(Sheu et al., 2010)	Taiwan	Retrospective/Observational	Cohort Study	14040
(Keating et al., 2021)	Multi Country	Retrospective/Observational	Cross Sectional Study	171
(Shipley et al., 2020)	Australia	Retrospective/Observational	Qualitative	19
(Shipley et al., 2018)	Australia	Retrospective/Observational	Qualitative	19
(Huang et al., 2015)	China	Retrospective/Observational	Cohort Study	350
(Marto et al., 2018)	Portugal	Retrospective/Observational	Cross Sectional Study	247
(Jones et al., 2020)	USA	Retrospective/Observational	Cohort Study	897
(Dardick et al., 2021)	USA	Retrospective/Observational	Cohort Study	449
(Sipila et al., 2018)	Finland	Retrospective/Observational	Cross Sectional Study	10,976
(Aznar et al., 2004)	Spain	Retrospective/Observational	Cross Sectional Study	49
(Quinn et al., 2014)	United Kingdom	Prospective	Qualitative	16
(Törnbom et al., 2019)	Sweden	Retrospective/Observational	Qualitative	11
(Karri & Ramasamy, 2019)	India	Retrospective/Observational	Cohort Study	186

(Jood et al., 2017)	Sweden	Retrospective/Observational	Case-Control Study	198
(Hassan et al., 2013)	India	Retrospective/Observational	Cross Sectional Study	46
(Tan et al., 2014)	Multi Country	Prospective	Cohort Study	218
(Nakagawa et al., 2017)	USA	Retrospective/Observational	NR	427
(Balci et al., 2011)	Turkey	Retrospective/Observational	Cross Sectional Study	192
(Kim et al., 2019)	USA	Retrospective/Observational	Case-Control Study	51
(Kisabay Ak et al., 2020)	Turkey	Retrospective/Observational	Cohort Study	60
(Wada et al., 2016)	Japan	Retrospective/Observational	Cross Sectional Study	4495
(Kulesh et al., 2021)	Russia	Retrospective/Observational	Cohort Study	126
(Ranellou et al., 2015)	Greece	Retrospective/Observational	Case-Control Study	51
(Skolarus et al., 2012)	USA	Retrospective/Observational	Cross Sectional Study	33917
(M'barek et al., 2021)	Tunisian	Retrospective/Observational	Case-Control Study	161
(Lannin et al., 2017)	Australia	Retrospective/Observational	Cohort Study	6526
(Leung & Caplan, 2016)	USA	Retrospective/Observational	Cohort Study	141
(Gungor et al., 2018)	Turkey	Retrospective/Observational	Cross Sectional Study	262
(Liang et al., 2021)	Australia	Prospective	Cohort Study	372
(Zhang et al., 2019)	China	Prospective	Cross Sectional Study	12
(Liu et al., 2021)	China	Retrospective/Observational	Cohort Study	50
(Cejas et al., 2019)	Argentina	Retrospective/Observational	Cross Sectional Study	78

(Rigal et al., 2007)	France	Prospective	Cross Sectional Study	100
(MacIntosh et al., 2021)	Canada	Retrospective/Observational	Cohort Study	8293
(Lawrence & Kinn, 2012)	United Kingdom	Retrospective/Observational	Cross Sectional Study	10
(Voorend et al., 2004)	Netherlands	Prospective	Case-Control Study	41
(Hackett et al., 2012)	Australia	Prospective	Cohort Study	271
(Alenljung et al., 2019)	Sweden	Prospective	descriptive qualitative study	10
(Aguilera-Pena et al., 2021)	Colombia	Retrospective/Observational	Cross Sectional Study	152
(Liang et al., 2018)	China	Retrospective/Observational	NR	93
(Hoffmann & Cases, 2008)	USA	Prospective	Cohort Study	26
(Baptista et al., 2010)	Portugal	Prospective	Cross Sectional Study	493
(Ou et al., 2018)	China	Retrospective/Observational	Case-Control Study	94
(Chraa et al., 2014)	Morocco	Retrospective/Observational	Cohort Study	128
(Mohammad S. Akhter et al., 2014)	India	Retrospective/Observational	Case-Control Study	100
(Mohd Suhail Akhter et al., 2014)	India	Prospective	Case-Control Study	100
(Akhter et al., 2017)	India	Prospective	Non-Randomiseze d Experimental (Quasi))	100
(Akhter et al., 2017)	India	Retrospective/Observational	Case-Control Study	100
(Si Larbi et al., 2021)	Saudi Arabia	Retrospective/Observational	Cohort Study	710
(Manning et al.)	Ireland	Prospective	NR	14
(Manning et al., 2021)	Ireland	Retrospective/Observational	Qualitative	14

(Saban et al., 2019)	Israel	Retrospective/Observational	Case-Series	NR
(Akram et al., 2018)	Pakistan	Retrospective/Observational	Cross Sectional Study	224
(Muller et al., 2014)	USA	Retrospective/Observational	Cohort Study	13
(Maaijwee et al., 2016)	Netherlands	Retrospective/Observational	Cohort Study	325
(Mahmutbegovic et al., 2020)	Bosnia	Prospective	Case-Control Study	40
(Zhang et al., 2020)	China	Retrospective/Observational	Case-Control Study	60
(Kinoshita et al., 2018)	Japan	Retrospective/Observational	Case-Control Study	516
(Martinez-Majander et al., 2021)	Finland	Prospective	Case-Control Study	136
(Martinez-Majander et al., 2021)	Finland	Prospective	Case-Control Study	347
(Kuybu et al., 2020)	USA	Retrospective/Observational	Cross Sectional Study	834,875
(Olibamoyo et al., 2019)	Nigeria	Retrospective/Observational	Cross Sectional Study	112
(Sajedi et al., 2017)	USA	Retrospective/Observational	NR	33
(Bonardo et al., 2018)	Argentina	Retrospective/Observational	Cohort Study	22
(Parekh et al., 2020b)	USA	Retrospective/Observational	Cross Sectional Study	161529
(Kersten et al., 2004)	United Kingdom	Retrospective/Observational	Cross Sectional Study	390
(Pöyhönen et al., 2020)	Finland	Prospective	Case-Control Study	30
(Pöyhönen et al., 2021)	Finland	Prospective	Case-Control Study	30
(Jin et al., 2018)	USA	Retrospective/Observational	Cohort Study	12,392
(Pirinen et al., 2021)	Finland	Retrospective/Observational	Case-Control Study	30
(Platts et al., 2006)	United Kingdom	Prospective	Case-Control Study	13

(Baghel et al., 2020)	India	Retrospective/Observational	NR	100
(Priya et al., 2021)	India	Retrospective/Observational	Cross Sectional Study	150
(Bahl et al., 2020)	United Kingdom	Retrospective/Observational	Cohort Study	167
(Fahmi & Elsaid, 2016)	Egypt	Prospective	NR	50
(Rhudy et al., 2020)	USA	Prospective	Cohort Study	30
(Vibo et al., 2021)	Estonia	Prospective	NR	437
(Belvís et al., 2007)	Spain	Prospective	Case-Control Study	39
(Steinicke et al., 2012)	Multi Country	Retrospective/Observational	Cross Sectional Study	2360
(O'Connor et al., 2011)	United Kingdom	Prospective	Cross Sectional Study	35
(Walters et al., 2020)	Multi Country	Retrospective/Observational	RCT	668
(García-Rudolph et al., 2021)	Spain	Retrospective/Observational	Cohort Study	130
(Rutkowski et al., 2021)	Canada	Prospective	Cohort Study	112
(Schneider et al., 2017)	Estonia	Retrospective/Observational	Cohort Study	837
(ŞEnadim et al., 2016)	Turkey	Retrospective/Observational	Cohort Study	11
(Shahid, 2019)	Saudi Arabia	Retrospective/Observational	Cohort Study	85
(Anderson & Whitfield, 2013)	Canada	Retrospective/Observational	Qualitative	9
(Zhang et al., 2014)	China	Prospective	Non-Randomiseze d Experimental (Quasi))	223
(Pahus et al., 2016)	Denmark	Retrospective/Observational	NR	685
(Schneider et al., 2020)	Estonia	Retrospective/Observational	Cohort Study	738
(Schneider et al., 2021)	Estonia	Retrospective/Observational	Case-Control Study	352
(Snögren & Sunnerhagen, 2009)	Sweden	Prospective	Cohort Study	71

(Oh et al., 2020)	Korea	Prospective	Cross Sectional Study	200
(Cain et al., 2021)	Multi Country	Retrospective/Observational	RCT	376
(Tsai et al., 2021)	Taiwan	Prospective	Cross Sectional Study	63
(Yu et al., 2016)	Australia	Retrospective/Observational	Cohort Study	359
(Opoku et al., 2020)	Ghana	Retrospective/Observational	Qualitative	10
(Tang et al., 2020)	China	Retrospective/Observational	Cohort Study	411
(Parekh et al., 2020a)	USA	Retrospective/Observational	Cross Sectional Study	43,860
(Hassan & Yarube, 2018)	Nigeria	Retrospective/Observational	Cross Sectional Study	47
(Kauranen et al., 2015)	Finland	Prospective	Cohort Study	230
(Tu et al., 2021)	Singapore	Prospective	Case-Series	18
(Tong et al., 2020)	USA	Retrospective/Observational	Cohort Study	1509203
(Patel et al., 2021)	USA	Retrospective/Observational	NR	198378
(De Giuli et al., 2019)	Italy	Prospective	NR	591
(Wolff et al., 2014)	France	Retrospective/Observational	Cross Sectional Study	159
(Wolff et al., 2015)	France	Prospective	NR	159
(Wolff et al., 2011)	France	Prospective	NR	48
(Montanaro et al., 2017)	Brazil	Retrospective/Observational	NR	134
(Montanaro et al., 2017)	Brazil	Retrospective/Observational	NR	134
(Moond et al., 2020)	India	Retrospective/Observational	Cohort Study	160
(Wang et al., 2014)	USA	Retrospective/Observational	Cohort Study	97374
(Xu et al., 2021)	China	Retrospective/Observational	Cross Sectional Study	249

(Xiao et al., 2021)	China	Retrospective/Observational	Cross Sectional Study	200
(Huang et al.)	China	Retrospective/Observational	Cohort Study	165
(Zhou et al., 2018)	China	Retrospective/Observational	NR	325
(Yang et al., 2021)	South Korea	Prospective	Cohort Study	152469
(Si et al., 2020)	China	Retrospective/Observational	Cross Sectional Study	343
(Yoon et al., 2021)	South Korea	Prospective	Cross Sectional Study	237
(Yue et al., 2019)	China	Retrospective/Observational	Case-Control Study	193
(Khan et al., 2018)	Pakistan	Retrospective/Observational	Cross Sectional Study	250
(Yuyang et al., 2021)	China	Retrospective/Observational	Case-Control Study	187

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