Imperial College London

A randomized controlled trial on ESSVR versus Usual Care

health data analytics and machine learning

Introduction to Statistical Thinking and Data Analysis

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A randomized controlled trial on ESSVR versus Usual Care

Abstract:

Background: Stroke brings severe obstacles to post-stroke patients' career. Therefore, a rehabilitation program: ESSVR was developed to help stroke patients return to work. In this study, we evaluated the influence of ESSVR on stroke patients going back to work and their overall health and life quality. Additionally, we investigated factors that can affect the completion of ESSVR.

Methods: A total of 1058 patients presenting for post-stroke rehabilitation treatment were enrolled in the trial. Participants were individually randomized 1:1 into either ESSVR (plus usual care) or usual care. Logistic regression models were fitted to analyze factors affecting the completion of ESSVR. The effect of ESSVR on stroke patients' returning to work was measured with cox regression models. The influence of ESSVR on participants' overall health condition and life quality was validated by applying linear regression models.

Results: Pre-stroke working status and severity of stroke were proven to be influential on stroke patients' completing ESSVR (OR Permanent vs casual = 2.034, P value =0.013; OR Self-Employed vs casual = 2.614, P value =0.013, OR Severe vs mils = 0.443, P value =0.002). Patients receiving ESSVR had a higher probability of returning to work (RR=2.407, $p<0.001$). However, the effect of ESSVR on patients' overall health and life quality was not significant. In contrast, demographic characteristics, pre-stroke working characteristics and stroke severity demonstrated more significant effects.

Conclusion: The results suggested the efficacy of ESSVR on stroke patients' returning to work. However, for patients' overall health and life quality, more factors should be considered.

1. Introduction:

Stroke is one of the most common causes of premature death in the UK with about 60,000 people each year undergoing a stroke each year. At the same time, the incidence of stroke is rising in young people. As estimated, nearly 40% strokes occurred among people of working age (18-69 years old).

What's disappointing is that a great number of survivors are suffering from sequela left by strokes such as cognitive impairment and disability, which brings obstacle to their returning to work. As is known, working is a promise to one's overall wellbeing, quality of life, social inclusion, and longevity. Therefore, returning to work should be one of the most significant goals for stroke survivors, but the truth is fewer than 50% of people return to work after stroke.

To help those stroke survivors get back to work, the program of Early Stroke Specialist Vocational Rehabilitation (ESSVR) has been established in England. ESSVR includes: (1) assessing the impact of the stroke on the person and their job; (2) educating individuals, employers, and families about the impact of the stroke on work, and strategies to reduce the impact; (3) work preparation and practice of work skills; and (4) meetings with employers and employment advisors to plan and monitor a phased return to work. However, the evidence for the effectiveness of ESSVR is limited, so a randomized controlled trail is needed to validate the benefit that ESSVR can bring to stroke survivors.

The first aim of the RCT is to evaluate the effect of pre-stroke working characteristics and stroke severity on stroke survivors' successful completion of the ESSVR program. And secondly, the primary aim of the trial is to evaluate whether ESSVR has a better effect than usual care on stroke survivors' returning to work and quality of life.

2. Methods:

2.1 Study design

The RCT on Early Stroke Specialist Vocational Rehabilitation (ESSVR) versus usual care was undertaken in four regions of England: North West, South East, West Midlands, and North East. A total of 1058 patients presenting for post-stroke rehabilitation treatment between 1 May 2020 and 30 November 2020 were enrolled. Participants were limited to those 18 to 69 years old and in work prior to experiencing the stroke. Participants were individually randomized 1:1 into either ESSVR (plus usual care) or usual care, interviewed each quarter and followed up for 1 year after randomization.

2.2 Data collection

Baseline data were collected including demographic characteristics (age, sex, and region of residence), pre-stroke working characteristics (working status, and number of working hours per week), and severity of stroke. Work participation after stroke was assessed every quarter, participants having returned to work reported the date when their work begun. At the final interview, about 12 months after randomization, an overall assessment on each participant's well-being and life quality was performed, and the information was encoded into health score, a standardized score reflecting their quality of life. For participants randomized to the ESSVR, the therapist also recorded if they had fulfilled the program.

23 patients returning to work failed to recall the date when they went back to work. Therefore, the interval from randomization to returning to work was imputed with the average one respectively for people receiving ESSVR or Usual care.

2.3 Statistics

In descriptive analysis, all results were expressed as the mean (standard deviation) for continuous variables, and count (percentage) for categorical variables. All the participants were grouped into ESSVR group or Usual care group, and individuals receiving ESSVR were further sub-grouped into the group completing the program or not completing the program. A t-test was applied to compare cross group difference in continuous variables, while a Chi-square test was applied for cross group difference comparisons in categorical variables.

For people randomized to the ESSVR, both simple logistic regression models and multiple logistic regression models adjusted for age and sex were fitted to analyse the effect of pre-stroke working characteristics (pre-stroke working status and pre-stroke working hours) and severity of stroke on the completion of ESSVR.

A cumulative hazard plot and a log rank test was applied to qualify whether ESSVR had a different effect on stroke patients' returning to work. Furthermore, for quantification the effect size, a cox regression model was fitted to evaluate how ESSVR influenced stroke patients' returning to work versus Usual care. A Global Schoenfeld test was applied to examine the proportional hazards assumption. As a result of randomization, demographic characteristics, pre-stroke working characteristics and severity of stroke were even across ESSVR and Usual Care group. Therefore, no confounder was included in the regression model. To make a sub-group analysis on sex and measure possible effect modification brought by demographic characteristics, pre-stroke working characteristics, and severity of stroke, a multiple Cox regression model was fitted. To respectively measure the effect of ESSVR on patients' returning to work in the first 6 month after randomization and second 6 month after randomization, a time split cox regression model was fitted.

To investigate the effect of ESSVR on participants' overall health condition and life quality, a simple linear regression model was fitted. We also measured other baseline variables' influence on patients' overall health condition with a simple linear regression model. Multiple linear regression models were applied for sub-group analysis on sex and for measurement of other variables' effect modification. We also applied a multiple regression model to evaluate the effect of ESSVR on patients' overall health condition adjusted for other covariates that were significantly associated with the outcome. Individuals' overall health condition was measured by health score, a standardized score reflecting their quality of life. Residual analysis of linear regression model was made by a normal Q-Q plot and a residuals versus fits plot.

Finally, since we noticed that some patients allocated to ESSCR failed to complete the program, we wanted to testify if our findings about ESSVR is still applicable to stroke patients who started with ESSVR but failed to complete it. Therefore, to investigate whether ESSVR still took effect on stroke patients who didn't complete ESSVR, a sensitivity analysis was made. A time-split cox regression l was fitted to compare returning to work across patients receiving usual care and patients who received ESSVR but didn't fulfil it.

All statistical analysis were performed with R 4.2.1 and $p<0.05$ was taken to indicate statistical significance.

3. Results:

3.1 Descriptive analysis

Baseline data including their demographic characteristics, pre-stroke working characteristics and severity of stroke were summarized in Table 1.

ESSVR group and Usual Care group showed no difference in demographic characteristics, pre-stroke working characteristics and severity of stroke, probably due to randomization. More participants in ESSVR group than Usual Care group returned to work in one year's follow up (91.5% versus 63.1%). In both Usual Care group and ESSVR group, most of the participants went back to work in the second 6 month instead of the first 6 month.

In ESSVR group, 379 individuals completed the program, while 162 individuals failed to complete the program. Across 2 groups of people, there was no significant difference in demographic characteristics,

patients' returning to work and their overall health score. However, the two groups significantly differed in pre-stroke working characteristics and severity of stroke.

Table 1: Descriptive analysis

		Usual Care (n=517)	*ESSVR (n=541)*	*P value*	*ESSVR (n=541)*		
					Not complete (n=162)	*Complete (n=379)*	*P value*
Sex (%)	Female	179 (34.6)	191 (35.3)	0.867	63 (38.9)	128 (33.8)	0.297
	Male	338 (65.4)	350 (64.7)		99 (61.1)	251 (66.2)	
Age (mean (SD))		59.74 (7.79)	60.17 (7.69)	0.369	61.06 (7.08)	59.78 (7.92)	0.077
Region in the UK (%)	North East	118 (22.8)	151 (27.9)	0.101	48 (29.6)	103 (27.2)	0.935
	North West	135 (26.1)	149 (27.5)		43 (26.5)	106 (28.0)	
	South East	122 (23.6)	122 (22.6)		35 (21.6)	87 (23.0)	
	West Midlands	142 (27.5)	119 (22.0)		36 (22.2)	83 (21.9)	
Pre-stroke working status (%)	Casual	74 (14.3)	71 (13.1)	0.559	29 (17.9)	42 (11.1)	0.026
	Contractor	52 (10.1)	71 (13.1)		23 (14.2)	48 (12.7)	
	FixedTerm	101 (19.5)	111 (20.5)		40 (24.7)	71 (18.7)	
	Permanent	220 (42.6)	221 (40.9)		56 (34.6)	165 (43.5)	
	Self Employed	70 (13.5)	67 (12.4)		14 (8.6)	53 (14.0)	
Pre-stroke working hours per week (mean (SD))		38.13 (10.19)	37.78 (10.35)	0.578	37.16 (10.51)	38.05 (10.28)	0.362
Severity of stroke (%)	Mild	228 (44.1)	223 (41.2)	0.538	59 (36.4)	164 (43.3)	0.004
	Moderate	216 (41.8)	231 (42.7)		64 (39.5)	167 (44.1)	
	Severe	73 (14.1)	87 (16.1)		39 (24.1)	48 (12.7)	
Return to work (%)		326 (63.1)	495 (91.5)	<0.001	145 (89.5)	350 (92.3)	0.359
health score (mean (SD))		39.77 (14.01)	40.89 (14.31)	0.196	40.91 (14.00)	40.88 (14.45)	0.982

3.2 Analysis on completion of ESSVR

In table 1, individuals completing or not completing the ESSVR show significant heterogeneity in pre-stroke working characteristics and severity of stroke. Therefore, logistic regression models were applied to study the effect of these factors on completing the ESSVR.

As table 2 shows, compared with causal work, permanent work and self-employed work had a significantly positive effect on the completion of ESSVR. People with permanent or self-employed work held more than 2 times higher probability of completing the ESSVR program ($OR_{\text{Permanent vs casual}} = 2.034$, P value =0.013; $OR_{\text{Self-Employed vs casual}} = 2.614$, P value =0.013). Additionally, people with severe stroke were 56% less likely to complete ESSVR than those with mild stroke ($OR_{\text{Severe vs mils}} = 0.443$, P value =0.002). Adjusted for age and sex, the effect of pre-stroke work status and severity of stroke on ESSVR remained significant ($OR_{\text{Permanent vs casual}} = 2.004$, P value =0.013; $OR_{\text{Self-Employed vs casual}} = 2.562$, P value =0.013; $OR_{\text{Severe vs mils}} = 0.411$, P value < 0.001).

Table 2: logistic regression analysis of the completion of ESSVR (n=541)

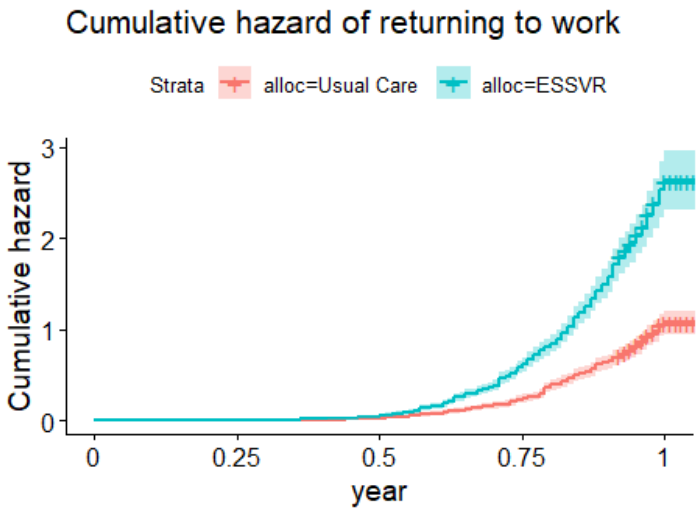
	Odds ratio	*95% CI of odds ratio*	*z value*	*p value*
(a) simple logistic regression				
a1. simple logistic regression: Completion of ESSVR ~ work_status_pre				
Contractor vs Casual	1.441	(0.727, 2.881)	1.043	0.297
FixedTerm vs Casual	1.226	(0.663, 2.260)	0.652	0.514
Permanent vs Casual	2.034	(1.155, 3.565)	2.477	0.013
Self Employed vs Casual	2.614	(1.245, 5.688)	2.493	0.013
a2. simple logistic regression: Completion of ESSVR ~ hpw_pre				
hpw_pre	1.008	(0.991, 1.026)	0.913	0.361
a3. simple logistic regression: Completion of ESSVR ~ stroke_severity				
Moderate vs Mild	0.939	(0.620, 1.420)	-0.299	0.765
Severe vs Mild	0.443	(0.264, 0.743)	-3.090	0.002
(b) multiple logistic regression adjusted for age and sex				
b1. multiple logistic regression: Completion of ESSVR ~ work_status_pre + age + sex				
Contractor vs Casual	1.343	(0.665, 2.732)	0.820	0.412
FixedTerm vs Casual	1.204	(0.649, 2.225)	0.592	0.554
Permanent vs Casual	2.004	(1.134, 3.522)	2.413	0.016
Self Employed vs Casual	2.562	(1.210, 5.619)	2.414	0.016
b2. multiple logistic regression: Completion of ESSVR ~ hpw_pre + age + sex				
hpw_pre	1.008	(0.990, 1.026)	0.843	0.399
b2. multiple logistic regression: Completion of ESSVR ~ stroke_severity + age + sex				
Moderate vs Mild	0.973	(0.640, 1.478)	-0.127	0.899
Severe vs Mild	0.411	(0.242, 0.695)	-3.318	<0.001

Work_status_pre: Pre-stroke working status(levels = Casaul workers, Contractor, FixedTerm, Permanent, Self-Employment);
hpw_pre: working hours per week prior to stroke;
stroke_severity: severity of stroke(levels=mild, severe, moderate);

3.3 Analysis on returning to work

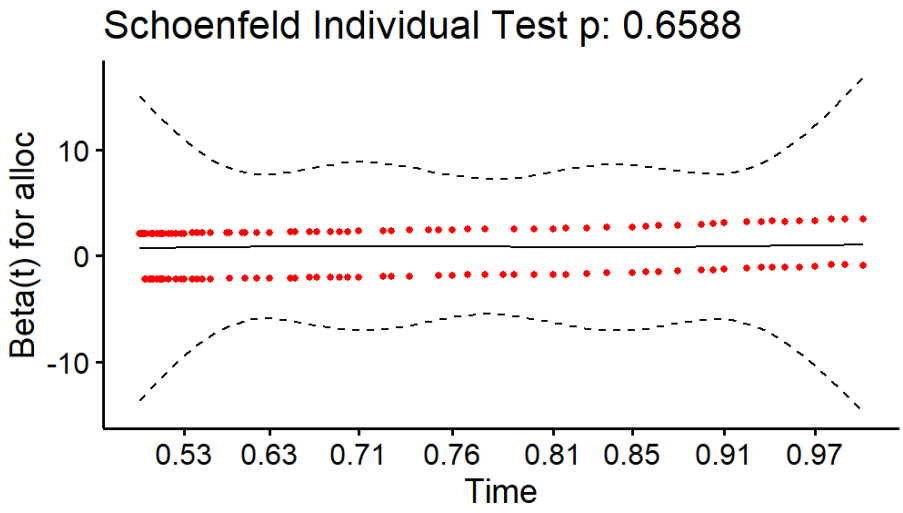
To begin with, cumulative hazard plot intuitively indicated different hazard of returning to work cross ESSVR group and Usual Care group. And the result of log rank test verified that ESSVR had a significantly different effect on stroke patients' returning to work (X^2=154, P value <0.001).

Plot1: cumulative hazard plot



According to the result of the Global Schoenfeld test, the proportional hazards assumption was met (Plot 2: P value = 0.6588)

Plot 2: Global Schoenfeld test



As showed by cox regression, by following up post-stroke patients for 1 year, stroke patients undergoing ESSVR were 64.2% more likely to go back to work compared with those receiving usual care (table3: RR=2.407, p<0.001). The effect of ESSVR on stroke patients' returning to work showed no different across male and female (table3(b) RR=1.101, p value=0.527). Effect modification by demographic characteristics, pre-stroke working characteristics, and severity of stroke was not found either.

By fitting a time-split cox regression model, the effect of ESSVR on returning to work in the first 6 months and second 6 months can be measured respectively. In the first 6 months, people undergoing ESSVR had 1.739 times higher probability of going back to work, but the effect was insignificant (HR=1.739, P value = 0.086). In the second 6 months, people receiving ESSVR had 2.446 times higher probability of returning to work, and the effect of ESSVR was significant (HR=2.446, P value < 0.001)

Table 3: cox regression analysis of the effect of ESSVR on returning to work (n=1058)

	hazard ratio	95% CI (hazard ratio)	z value	p value
(a) Simple cox regression : Return to work ~ Alloc				
Alloc: ESSVR vs Usual Care	*2.407*	*(2.087, 2.774)*	*12.100*	*<0.001*
(b) Multiple cox regression: Return to work ~ Alloc * Sex				
*Alloc: ESSVR vs Usual Care*Sex:Male vs female*	*1.101*	*(0.818, 1.481)*	*0.633*	*0.527*
(c) Multiple cox regression: Return to work ~ Alloc * Age				
*alloc:ESSVR*age*	*1.017*	*(0.999, 1.035)*	*1.861*	*0.063*
(d) Multiple cox regression: Return to work ~ Alloc * work_status_pre				
*Alloc: ESSVR vs Usual Care*work_status_pre: Contractor vs Casual*	*0.962*	*(0.552, 1.678)*	*-0.136*	*0.892*
*Alloc: ESSVR vs Usual Care*work_status_pre: FixedTerm vs Casual*	*0.788*	*(0.472, 1.315)*	*-0.911*	*0.362*
*Alloc: ESSVR vs Usual Care*work_status_pre: Permanent vs Casual*	*1.062*	*(0.689, 1.638)*	*0.274*	*0.784*
*Alloc: ESSVR vs Usual Care*work_status_pre: Self-Employed vs Casual*	*0.890*	*(0.517, 1.532)*	*-0.422*	*0.673*
(e) Multiple cox regression: Return to work ~ Alloc * hpw_pre				
*Alloc: ESSVR vs Usual Care * hpw_pre*	*1.006*	*(0.993, 1.020)*	*0.890*	*0.373*
(f) Multiple cox regression: Return to work ~ Alloc * stroke_severity				
*Alloc: ESSVR vs Usual Care*stroke_severity:Moderate vs mild*	*1.019*	*(0.754, 1.376)*	*0.122*	*0.903*
*Alloc: ESSVR vs Usual Care*stroke_severity: Severe vs mild*	*0.8827*	*(0.567, 1.373)*	*-0.553*	*0.580*
(g) Time split cox regression: Return to work ~ Alloc * ftime				
Alloc: ESSVR vs Usual Care (ftime: 1st6mon)	1.739	(0.925, 3.269)	1.718	0.086
*Alloc: ESSVRvs Usual Care * ftime: 2nd 6month vs 1st 6month*	1.406	(0.736, 2.689)	1.033	0.302
Alloc: ESSVR vs Usual Care (ftime: 2nd6mon)	*2.446*	*(2.114, 2.830)*	*1.203*	*<0.001*

Alloc: allocation of rehabiliation program (levels = Usual Care, ESSVR);
Work_status_pre: Pre-stroke working status(levels = Casaul workers, Contractor, FixedTerm, Permanent, Self-Employment);
hpw_pre: working hours per week prior to stroke;
stroke_severity: severity of stroke(levels=mild, severe, moderate);
ftime: time interval of follow-up(levels = 1st 6 months, 2nd 6 months)

3.4 Analysis on overall health (health score)

Overall health and life quality of post-stroke patients was measured by health score. As demonstrated in the simple linear regression model (table 4), people receiving ESSVR had 1.127 higher overall scores than people receiving usual care, but the effect is not significant (β = 1.127, P value =0.196). Sex, age, region of residence, pre-stroke working status and severity of stroke had a significant effect on patients' overall score. On average, the health scores of males were lower than females' by 4.237(β =-4.237, P value < 0.001). Older people were overall less healthy after stroke than young ones (β =-0.166, P value = 0.003). People living in the Northwest of the UK had lower health scores by 2.74 (p=0.023) than those living in Northeast. The health scores of self-employed people were lower than causal workers by 3.34. Compared with people with mild stroke, people undergoing moderate stroke had significant lower health scores by 4.489, while the health of people experiencing severe stroke was worse (β =-8.919, P value = 0.196).

Table 4: Simple linear regression analysis on health score

	estimate	*95% CI of estimate*	*t value*	*p value*
(a) simple linear regression: health score ~ alloc				
alloc: ESSVR vs Usual care	1.127	(-0.582, 2.836)	1.294	0.196
(b) simple linear regression: health score ~ sex				
sex: Male vs Female	-4.237	(-6.011, -2.462)	-4.685	<0.001
(c) simple linear regression: health score ~ age				
age	-0.166	(-0.276, -0.056)	-2.955	0.003
(d) simple linear regression: health score ~ region				
region: North West vs North East	-2.740	(-5.101, -0.379)	-2.277	0.023
region: South East vs North East	-0.270	(-2.724, 2.183)	-0.216	0.829
region: West Midlands vs North East	-0.578	(-2.989, 1.834)	-0.470	0.638
(e) simple linear regression: health score ~ work_status_pre				
work_status_pre: Contractor vs Casual	-3.340	(-6.746, 0.066)	-1.924	0.055
work_status_pre: FixedTerm vs Casual	-2.321	(-5.315, 0.673)	-1.521	0.129
work_status_pre: Permanent vs Casual	-2.006	(-4.666, 0.653)	-1.480	0.139
work_status_pre: SelfEmployed vs Casual	-3.323	(-6.634, -0.013)	-1.970	0.049
(f) simple linear regression: health score ~ hpw_pre				
hpw_pre	-0.083	(-0.166, 0.001)	-1.948	0.052
(g) simple linear regression: health score ~ stroke_severity				
stroke_severity: Moderate vs mild	-4.489	(-6.299, -2.679)	-4.866	<0.001
stroke_severity: Severe vs mild	-8.919	(-11.414, -6.423)	-7.013	<0.001

Alloc: allocation of rehabiliation program (levels = Usual Care, ESSVR);
Region: region of residence(levels = North West, South East, West Midlands, North East region);
Work_status_pre: Pre-stroke working status(levels = Casaul workers, Contractor, FixedTerm, Permanent, Self-Employment);
hpw_pre: working hours per week prior to stroke;
stroke_severity: severity of stroke(levels=mild, severe, moderate);

Pre-specified sub-group analysis by sex was conducted by a multiple regression model with an interaction item of sex and rehabilitation program (ESSVR vs Usual Care). It turned out that the effect of ESSVR on health didn't significantly differ across male and female (P value = 0.782). In addition, as showed in table 5, all the p values of interaction items in multiple linear regression models were more than 0.05. Therefore, effect modification on the association between rehabilitation program and health score were not found.

Table 5: Multiple linear regression analysis for effect modification on health score

	estimate	95% CI of estimate	t value	p value
(a) multiple linear regression: health score ~ alloc*sex				
alloc: ESSVR vs Usual care * sex: Male vs Female	0.500	(-3.051, 4.051)	0.276	0.782
(b) simple linear regression: health score ~ alloc*age				
alloc: ESSVR vs Usual care * age	0.129	(-0.091, 0.349)	1.150	0.251
(d) simple linear regression: health score ~ alloc*region				
alloc: ESSVR vs Usual care vs * region: North West vs North East	0.945	(-3.795, 5.685)	0.391	0.696
alloc: ESSVR vs Usual care vs * region: South East vs North East	2.992	(-1.929, 7.913)	1.193	0.233
alloc: ESSVR vs Usual care vs * region: West Midlands vs North East	-1.827	(-6.673, 3.02)	-0.740	0.460
(e) simple linear regression: health score ~ alloc*work_status_pre				
alloc: ESSVR vs Usual care * work_status_pre: Contractor vs Casual	1.922	(-4.935, 8.779)	0.55	0.582
alloc: ESSVR vs Usual care * work_status_pre: FixedTerm vs Casual	-2.474	(-8.466, 3.517)	-0.81	0.418
alloc: ESSVR vs Usual care * work_status_pre: Permanent vs Casual	-2.283	(-7.603, 3.037)	-0.842	0.400
alloc: ESSVR vs Usual care * work_status_pre: SelfEmployed vs Casual	-3.121	(-9.743, 3.501)	-0.925	0.355
(f) simple linear regression: health score ~ alloc*hpw_pre				
alloc: ESSVR vs Usual care * hpw_pre	0.077	(-0.09, 0.243)	0.904	0.366
(g) simple linear regression: health score ~ alloc*stroke_severity				
alloc: ESSVR vs Usual care * stroke_severity: Moderate vs mild	0.213	(-3.41, 3.835)	0.115	0.908
alloc: ESSVR vs Usual care * stroke_severitySevere vs mild	-0.266	(-5.273, 4.74)	-0.104	0.917

Alloc: allocation of rehabiliation program (levels = Usual Care, ESSVR);
Region: region of residence(levels = North West, South East, West Midlands, North East region);
Work_status_pre: Pre-stroke working status(levels = Casaul workers, Contractor, FixedTerm, Permanent, Self-Employment);
hpw_pre: working hours per week prior to stroke;
stroke_severity: severity of stroke(levels=mild, severe, moderate);

To investigate the independent effect of ESSVR on overall health and quality of life adjusted by other factors, a multiple regression model is fitted adjusted for sex, age, region, pre-stroke working status and severity of stroke. It turned out that adjusted for sex, age, region, pre-stroke working status and severity of stroke, people receiving ESSVR had higher health scores by 1.445 (β =1.445, P value = 0.087). After adjustment, sex, age, and stroke severity remained to be independently effective factors to health scores.

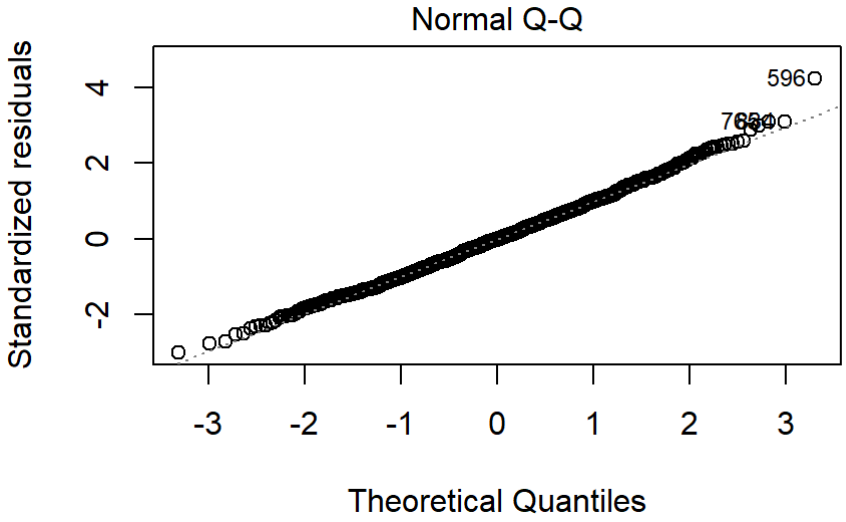
Table6： Multiple linear regression model on health score

	estimate	*95% CI of estimate*	*t value*	*p value*
(a) multiple linear regression: health score ~ alloc + sex + region + work_status_pre + stroke_severity				
alloc: ESSVR vs Usual care	1.445	(-0.210, 3.100)	1.713	0.087
sex: Male vs Female	-3.608	(-5.395, -1.821)	-3.961	<0.001
age	-0.175	(-0.282, -0.068)	-3.212	0.001
region: North West vs North East	-2.028	(-4.315,0.26)	-1.740	0.082
region: South East vs North East	0.406	(-1.971,2.782)	0.335	0.738
region: West Midlands vs North East	0.094	(-2.248,2.435)	0.078	0.937
work_status_pre: Contractor vs Casual	-1.700	(-5.043,1.644)	-0.998	0.319
work_status_pre: FixedTerm vs Casual	-2.197	(-5.089,0.694)	-1.491	0.136
work_status_pre: Permanent vs Casual	-1.272	(-3.848,1.304)	-0.969	0.333
work_status_pre: SelfEmployed vs Casual	-2.355	(-5.573,0.863)	-1.436	0.151
stroke_severity: Moderate vs mild	-4.273	(-6.073,-2.473)	-4.658	<0.001
stroke_severity: Severe vs mild	-8.439	(-10.924,-5.954)	-6.664	<0.001

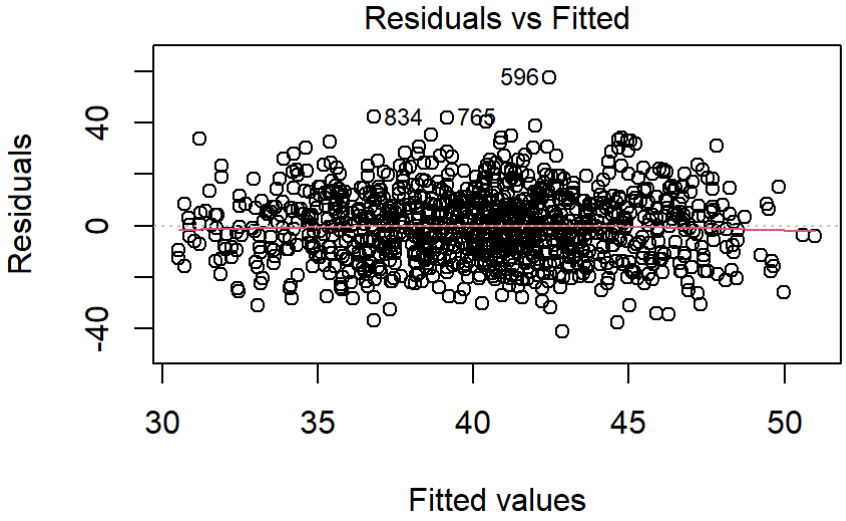
Alloc: allocation of rehabiliation program (levels = Usual Care, ESSVR);
Region: region of residence(levels = North West, South East, West Midlands, North East region);
Work_status_pre: Pre-stroke working status(levels = Casaul workers, Contractor, FixedTerm, Permanent, Self-Employment);
stroke_severity: severity of stroke(levels=mild, severe, moderate);

Finally, as the Normal Q-Q plot (plot 3) and the residuals versus fits plot (plot 4) showed, linear regression assumptions on residuals were robust.

Plot 3: QQ plot of adjusted multiple linear model



Plot 4: residuals versus fits plot of adjusted multiple linear model



3.5 Sensitivity analysis

A time split cox regression model was fitted to compare the hazard of returning to work across patients receiving usual care and patients who received ESSVR but didn't fulfil it. As table7 showed, in the second 6 months, the effect of ESSVR on returning to work was still significant (HR=2.116, P value<0.001).

Table 7: sensitivity analysis (n=679)

	hazard ratio	*95% CI (hazard ratio)*	*z value*	*p value*
(a) Time split cox regression: Return to work ~ Alloc * ftime				
Alloc: ESSVR vs Usual Care (ftime: 1st6mon)	2.379	(1.093, 5.180)	2.184	0.029
*Alloc: ESSVRvs Usual Care * ftime: 2nd 6month vs 1st 6month*	*0.890*	(0.398, 1.988)	-0.285	0.775
Alloc: ESSVR vs Usual Care (ftime: 2nd6mon)	*2.116*	*(1.726, 2.595)*	*7.204*	<0.001

Alloc: allocation of rehabiliation program (levels = Usual Care, ESSVR);
ftime: time interval of follow-up(levels = 1st 6 months, 2nd 6 months)

4. Discussion

In the present study, we showed that stroke patients receiving ESSVR were more likely to return to work. Therefore, it will be helpful if ESSVR can be provided to post stroke patients of working age as a routine rehabilitation. What's interesting is that in the second 6 months after receiving ESSVR, ESSVR demonstrated significant effect on patients' returning to work, while in the first 6 month, the effect of ESSVR was not significant. This finding suggested that ESSVR should last for 1 year to be effective for stroke patients' returning to work.

Although ESSVR can help with stroke patients' returning to work, it didn't show significant influence on patients' overall health and quality of life. In contrast, other factors like sex, age, and severity of stroke were more associated with patients' overall health and life quality. Male, older people, and patients undergoing severer stroke reported worse health condition and quality of life, so additional care and financial support can be given to them.

In addition, to investigate why ESSVR failed to significantly promote patients' overall health and life quality, quality of post-stroke patients' work should be evaluated like their income, working status, working hours and etc. Not only returning to work, but we also need to measure the effect of ESSVR on the quality of their work, which may affect their overall health and life quality. Only in this way can we suggest more proper intervention with ESSVR.

Finally, it's always important to help patients complete ESSVR if they have chosen the rehabilitation. As our study suggested, people with casual work were less likely to finish the rehabilitation program than those self-employed or those with permanent work. Also, people undergoing severe stroke didn't perform well at completing ESSVR. Therefore, further study is needed to understand reasons why those population are more likely to drop from ESSVR program.