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RESEARCH ARTICLE

Heterogeneity in Cost-Effectiveness Analysis of Vaccination for Mild and Moderate Alzheimer's Disease

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Abstract: ***Background*:** Immunotherapy for Alzheimer's disease(AD) has gained momentum in recent years. One of the concerns over its application pertains to Cost-Effectiveness Analysis (CEA) from population average and specific subgroup differences, as such a therapy is imperative for health decision-makers to allocate limited resources. However, this sort of CEA model considering heterogeneous population with risk factors adjustment has been rarely addressed.

***Methods*:** We aimed to show the heterogeneity of CEA in immunotherapy for AD in comparison with the comparator without intervention. Economic evaluation was performed *via* incremental Cost-Effectiveness Ratio (ICER) and Cost-Effectiveness Acceptability Curve (CEAC) in terms of the Quality-Adjusted Life Years (QALY). First, population-average CEA was performed with and without adjustment for age and gender. Secondly, sub-group CEA was performed with the stratification of gender and age based on Markov process.

***Results*:** Given the threshold of $20,000 of willingness to pay, the results of ICER without and with adjustment for age and gender revealed similar results ($14,691/QALY and $17,604/QALY). The sub-group ICER results by different age groups and gender showed substantial differences. The CEAC showed that the probability of being cost-effective was only 48.8%-53.3% in terms of QALY at population level but varied from 83.5% in women aged 50-64 years, following women aged 65-74 years and decreased to 0.2% in men≥ 75 years.

***Conclusion*:** There were considerable heterogeneities observed in the CEA of vaccination for AD. As with the development of personalized medicine, the CEA results assessed by health decision-maker should not only be considered by population-average level but also specific sub-group levels.

Keywords: Alzheimer's disease, immunotherapy, vaccination, cost-effectiveness analysis, heterogeneity, personalized medicine .

1. INTRODUCTION

Alzheimer's disease (AD) is the most common dementia among the elderly. Currently, it is still a chronic progressive neurodegenerative condition accounting for increased health burden [1]. Decision-makers face this challenging issue about the coverage of health care system and the investment for the future research in the area of AD. Due to growing disease burden of AD, many new drugs are in the pipeline and a new therapy strategy is developing although the efficacy of disease modifying treatments (DMTs) in curing AD is still lacking [2].

The devastating economic burden prompts the policy makers to pay attention to Cost-Effectiveness Analysis (CEA). AD medications are found either to dominate standard therapy or to be more costly but effective than standard treatment [3]. Recently, the basic research of AD showed that immunotherapy has the potential of modifying disease progression [4]. The previous CEA study also demonstrated that immunotherapy for AD was cost-effectiveness in gaining life years compared with non-vaccination [5]. Because the course of AD development is heterogeneous, risk factors accounting for its progression have been considered in many AD progression models. However, most CEA studies did not

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take these risk factors into consideration. A recent review of economic evaluation claimed that the development of methods to model Alzheimer's disease is slow, especially compared to cancer and cardiovascular diseases [6]. In addition, evidence-based medicine relying on good quality of a randomized controlled trial has also evolved into personalized medicine, namely, precision medicine [7]. The emphasis is not placed on the mean value level but on sub-group or individual level because of the stat-of-the-art discovery on individual variation due to genetic variants, epigenetic markers, new detrimental factors, new health care intervention, and new treatments and therapies.

Nowadays, genome-wide association studies have identified more than 20 genetic loci associated with the risk of AD [8]. The recent two independent epigenome-wide association studies of AD suggested that epigenetic changes associated more to AD than expected [9]. The development of biomarkers also pointed out that AD progression might occur years before diagnosis, which supports the active prevention strategy in younger and healthier subgroups [10]. Although the current clinical trials of immunotherapy of AD have failed to show significant efficacy, scientific societies still focus on and have high expectations with the development of immunotherapy. We herein discuss and try to find the new target of mechanism, right drug or appropriate clinical trial design that may respond to the current challenges of the immunotherapy for AD [11, 12]. When new powerful and effective immunotherapies are available, not only recognizing AD in a very early stage but also treating a special subgroup is essential [13]. Meanwhile, Golde *et al*. also pointed the possible prevention framework to select the right time for the right drug for AD [14]. Therefore, advance in the model of AD progression, which incorporates heterogeneity and uncertainty would be a guidance for both clinical and healthy policy decision makers.

It is also important for decision maker to know how to allocate limited resources to specific subgroups in the area of personalized medicine. Therefore, the aim of this study was to assess the heterogeneity of cost-effectiveness in immunotherapy for AD in comparison with the comparator in the absence of intervention.

2. MATERIAL AND METHODS

2.1. Markov Decision Model

The cohort of CERAD (70.8 ± 0.8 years of age) was composed of 40% male, and 17% were 50-65 years of age, 38% were 65-74 years of age and 45% were 75 or older. The four states were followed up by different outcomes: mild, moderate, severe, and death. The disease progression to different statues changed with time. We constructed a Markov model (Fig. **1**) to estimate the annual transition rates between the states by using published data from previous studies (see Appendix).

We assumed that the cohort consisted of 50% mild state and 50% moderate state. The intervention of active immunization was compared with unvaccinated group. Moreover, the duration of protection offered by vaccine was assumed to persist during 10 years. The efficacy of vaccine was estimated from our previous study [5]. The covariates from the previous studies of Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [15] were adopted to illustrate the heterogeneity of CEA.

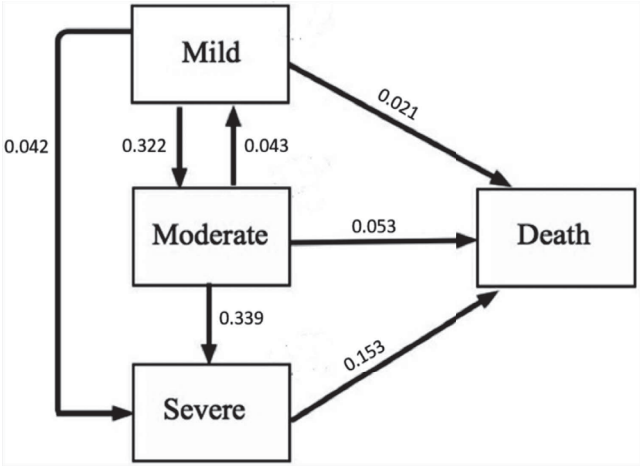

Fig. (1). Markov model with annual transition rate for nature history of Alzheimer's disease.

2.2. Cost-Effectiveness Analysis for the Average Population

The transition probability of different status was adopted from the CERAD cohort and Dirichlet distributions were assigned according to the 345 participants of CERAD initially (Table **1**). Probability cost-effectiveness analysis was performed by using Bayesian Monte Carlo simulation. A total of 5000 simulations were performed. The outcome measure was Quality-Adjusted Life Year (QALY). The threshold of willingness to pay (WTP) was set at $US 20,000 per QALY or per life year gained referring to the average Gross Domestic Product per Capita in 2011 in Taiwan. The CEA was performed from a societal perspective. The direct costs included the medical expenses paid by National Health Insurance and out-of-pocket payments. The indirect costs mainly included caregiver time, which was calculated by opportunity cost of time and replacement cost [16]. The costs were assumed to be dependent on the severity of clinical stage of AD. Accordingly, they were not changed across the different groups. We used the utility scores from Neumann's study, which measured QALY *via* the Health Utilities Index Mark II (HUI:2) [17]. All the costs and effectiveness were discounted at 3% annually and series of ICERs were plotted in the cost-effectiveness (C-E) plane and the probability of being cost-effective was also plotted with Cost-Effectiveness Acceptability Curve (CEAC).

2.3. Heterogeneity of Cost-Effectiveness Analysis

We applied a Markov regression model with age and gender as covariates to capture the annual baseline hazard rate by Cox proportional hazard model in each transition [18]. Accordingly, the transition probability would be a function of the transition rate with age and gender. The heterogeneities were illustrated by the results for the six subgroups: female with aged 50-64 years (Group 1; GP1), female with aged 65-74 years (Group 2; GP2), female with aged ≥75 years (Group 3; GP3), male with aged 50-64 years

Table 1. Base-case estimate and distribution of parameters for probabilistic sensitivity analysis.

Variable	Base case estimate	Distribution
Transition probability		
Mild to moderate	0.322	Dirichlet (122.8, 64.4, 8.4, 4.2)
Mild to severe	0.042	
Mild to death	0.021	
Moderate to mild	0.043	Dirichlet (5.676, 74.58, 44.748, 6.996)
Moderate to severe	0.339	
Moderate to death	0.053	
Severe to death	0.153	Dirichlet (0, 0, 7.623, 1.377)
Costs		
Medical cost of mild	1,266	Triangular (633, 1266, 2533)
Care cost of mild	8,996	Triangular (4498, 8996, 17992)
Medical cost of moderate	1,298	Triangular (649, 1298, 2596)
Care cost of moderate	17,593	Triangular (8797, 17593, 35187)
Medical cost of severe	1,586	Triangular (793, 1586, 3173)
Care cost of severe	24,367	Triangular (12184, 24367, 87350)
QALY		
Mild	0.68	Beta (26.98, 12.69)
Moderate	0.54	Beta (24.45, 20.83)
Severe	0.37	Beta (8.84, 15.06)

QALY: Quality adjusted life year

(Group 4; GP4), male with aged 65-74 years (Group 5; GP5), and male with aged ≥75 years (Group 6; GP6).

3. RESULTS

3.1. Cost-Effectiveness Analysis in Homogeneous Population

Table **2** shows the result of CEA with distribution assignment and Monte Carlo simulation. The results for 10 years of follow-up show that treatment in the vaccinated group gained 0.372 QALYs but costed more *i.e*., up to $5,465. The ICER for vaccinated group was $14,691 per QALY gained. After adjustment for age and gender, 0.376 QALYs was gained with additional $6,619. The ICER for vaccinated group was $17,604 per QALY gained. The absolute values of cost and effectiveness were mildly elevated and the ICER values increased a little after adjustment for age and gender.

Fig. (**2A**) shows the result of Monte Carlo simulation with C-E plane. In terms of QALY, the probability of being cost-effective in the vaccinated group was 46.5% given the WTP threshold of $20,000 compared to the unvaccinated group over 10 years. (Fig. **2B**) shows after adjustment for age and gender, 51.9% the ICER simulated points were located below the threshold of WTP threshold of $20,000 compared to the unvaccinated group.

According to the CEAC of QALY, the probability of being cost-effectiveness for vaccinated group was 48.8% at WTP of $20,000 in population average and 53.3% in Markov regression model with adjustment for age and gender (Fig. **3**).

3.2. Heterogeneities of CEA in Different Subgroups

Table **3** shows the CEA of the group in different age group and gender. In terms of women, vaccination trades were $7,209 per QALY in 50-64 years; $9,734 per QALY in 65-74 years and $22,627 per QALY in more than 75 years group. In men, treatment trades were $26,712 per QALY in 50-64 years; $27,746 per QALY in 65-74 years and $27,746 per QALY in aged ≥75 years.

On C-E plane, the percentage of simulated ICER points of QALY in women below the threshold decreases from 83.08% in GP1 to 36.04% in GP3 (Fig **4A**-**4C**). In men, it further decreases to 13.96% in GP4 to 0.12% in GP6 (Fig. **4D**-**4F**). Table **4** shows the probability of being cost-effective under WTP of $20,000 in different models and subgroups according to the CEAC.

Table 2. Homogenous Cost-effectiveness analysis of follow-up 10 years after vaccination.

	Cost ($US)	Effectiveness	C/E[b]	ICER[c]
Average population				
QALY[a]				
Vaccine	194,287	3.032	64,079	14,691
No vaccine	188,822	2.66	70.986	
Age-and-gender adjustment				
QALY[a]				
Vaccine	205,731	3.213	64,031	17,604
No vaccine	199,112	2.837	70,184	

[a]QALY: Quality-adjusted life year
[b]C/E: cost per QALY
[c]ICER=Incremental cost-effectiveness ratio

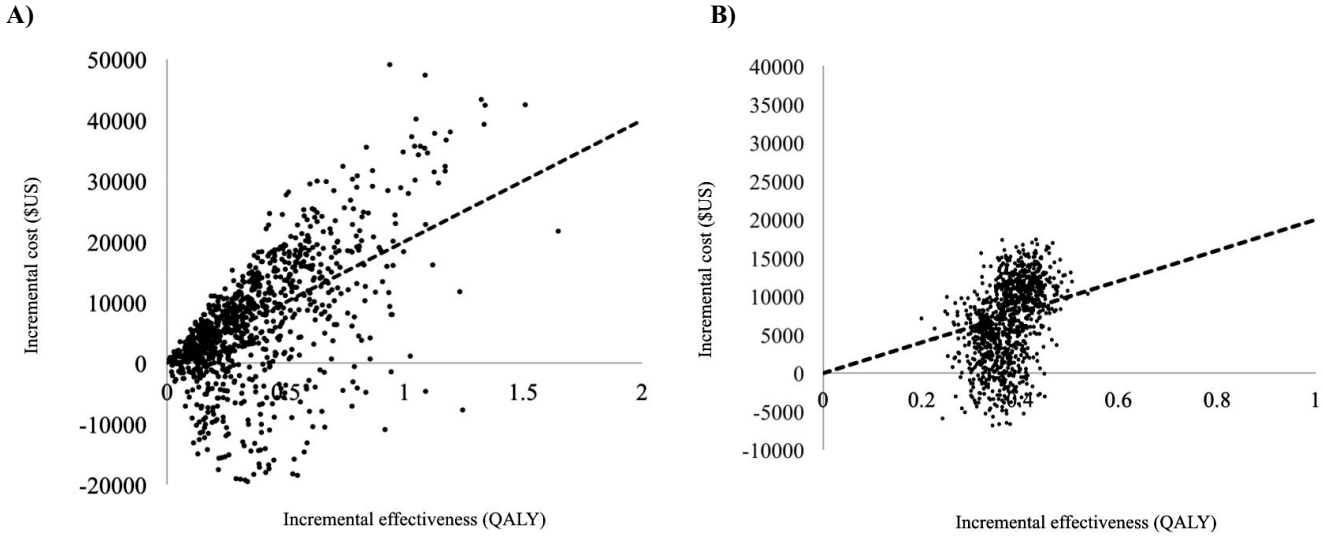

Fig. (2). A. Simulated results of the cost-effectiveness plane for quality-adjusted life year (QALY) (**A**) Average Population. **B.** Simulated results of the cost-effectiveness plane for quality-adjusted life year (QALY) (**B**) Average population with age-and-gender adjustment.

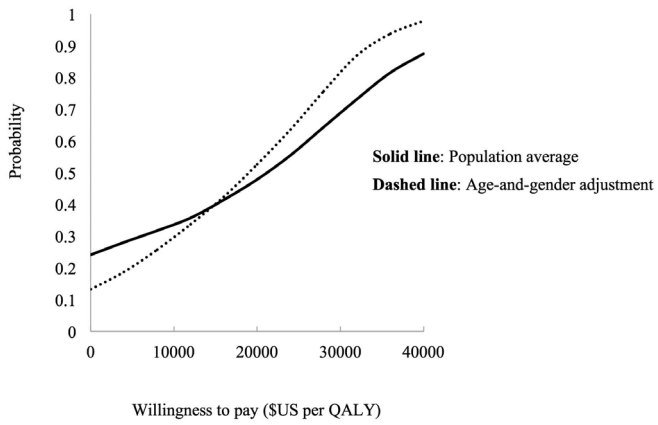

Fig. (3). Cost-effectiveness acceptability curve of vaccination for 10 years.

4. DISCUSSION

To the best of knowledge, this is the first study presenting the variation of CEA in specific group compared to the population average in terms of active immunization of AD. Furthermore, we also explored the heterogeneity in CEA. In the simulated study of active immunization for AD, although at the threshold of $20,000, the probability of being cost-effective in population average was only 48.8%-53.3% in terms of QALY, we found that it would be the most cost-effectiveness for the women of 50-64 years age (83.5% at WTP of $20,000).

We found that the ICER of QALY for 10-years was $14,691 and $17,604 in average population and Markov regression models with adjustment for age and gender, respectively. The CEAC of these two models (Fig. **3**), the probabilities of being cost-effective given WTP $20,000 are very close (48.8% and 53.3% for population average and Markov regression model with age and gender adjustment, respec-

Table 3. Cost-effectiveness of the specific subgroups.

-	Women				Men			
	C($)	E	C/E[b]	ICER[c]	C	E	C/E[b]	ICER[c]
50-64 years of age								
GP1	-	-	-	-	**GP4**	-	-	-
Vaccine	227,458	3.399	66,919	7,209	206,524	3.03	68,160	26,712
No vaccine	225,014	3.06	73,534		196,026	2.637	74,337	
65-74 years of age								
GP2	-	-	-	-	**GP5**	-	-	-
Vaccine	215,064	3.383	63,572	9,734	190,854	2.958	64,521	27,746
No vaccine	211,628	3.03	69,844		179,589	2.552	70,372	
≥ 75 years of age								
GP3	-	-	-	-	**GP6**	-	-	-
Vaccine	183,680	3.091	59,424	22,627	151,310	2.537	59,641	36,023
No vaccine	174,652	2.692	64,878		135,712	2.104	64,502	

GP1 (Group 1): Female with aged 50-64 years; GP2 (Group 2): Female with aged 65-74 years; GP3 (Group 3): Female with aged ≥75 years; GP4 (Group 4): Male with aged 50-64 years; GP5 (Group 5): Male with aged 65-74 years; GP6 (Group 6): Male with aged ≥75 years.
C: cost; E: effectiveness, QALY (Quality-adjusted life year),
[b] C/E: cost per QALY
[c] ICER=Incremental cost-effectiveness ratio

tively) but go separate ways given other different WTPs. These results imply that the conventional CEA approach can only make average estimation, but ignores the subgroup heterogeneity. Or to put it another way, after dealing with second order uncertainty by defining probability distribution of parameters and sampled jointly by Monte Carlo simulation, conventional CEA is not sufficient for presenting the subgroup heterogeneity of CEA.

Where there is evidence of heterogeneity, appropriate factors should be carefully considered into CEA. In a nature history of AD, the heterogeneity arises from the baseline hazards, which are affected by the gender and gender in this study. When we divided the whole population into six subgroups from Markov regression model, there were huge heterogeneities in the probability of being cost-effective given the threshold of $20,000 (see Table **3** and **4**). If the policy maker makes the decision according to the result of average population level, the treatment might be regarded as not very cost-effectiven because the probability of being cost-effective is only 48.8%-53.3% in terms of QALY. The decision making by heterogeneity of cost-effectiveness analysis can be optimized, which has been demonstrated in our findings. However, the subgroup analysis showed that the probability of being cost-effective regarding QALY is the highest in women aged 50-64 years followed by women aged 65-74 years. In contrast, from the perspective of individual, the decision about whether to afford new vaccination may take the results of subgroup analysis into consideration.

There are significant gender differences in the epidemiology profile of AD. The prevalence of AD is significantly higher in women. It might be due to life expectancy or estrogen receptor β genetic polymorphism in the regulation of neurological health [19]. Some studies showed women to have a faster rate of decline after the diagnosis of AD [20] and mild cognitive impairment [21]. This is different from the data of this study, which was extracted from CERAD database. Previous studies of CERAD reported that men had higher hazard of the moderate-to-death and severe-to-death transitions (P>0.05) [15]. This might due to different ethnicity or demographic characteristics. Basically, the patients of AD have the same clinical symptoms and histopathology feature of age of onset. However, the early onset AD might be a distinct subgroup [22]. It has greater cognitive deterioration although the apolipoprotein (APOE) ε4 alleles is more likely to be found in late onset AD [23]. Similarly, more rapid cognitive decline in patients with early-onset AD was also reported in CERAD database. Younger patients also performed more poorly constructional praxis task over time than older patients [24]. The interaction of age and gender for AD should also be considered. A large meta-analysis reported the effect of APOE ε4 allele to be more pronounced in women and associated with AD highest at the age of 60 years in Caucasian men and women [25]. In a recent review, reporting gender differences in all aspects of AD is crucial and encouraged for the era of precision medicine in AD [26]. Because there are many evidences supporting the different nature of AD in gender and age group, it would be appropriate to incorporate these factors into CEA.

These figures revealed there might be some specific subgroup existing, which could not get the benefit from vaccination. For example, the development of AN1792 halted at

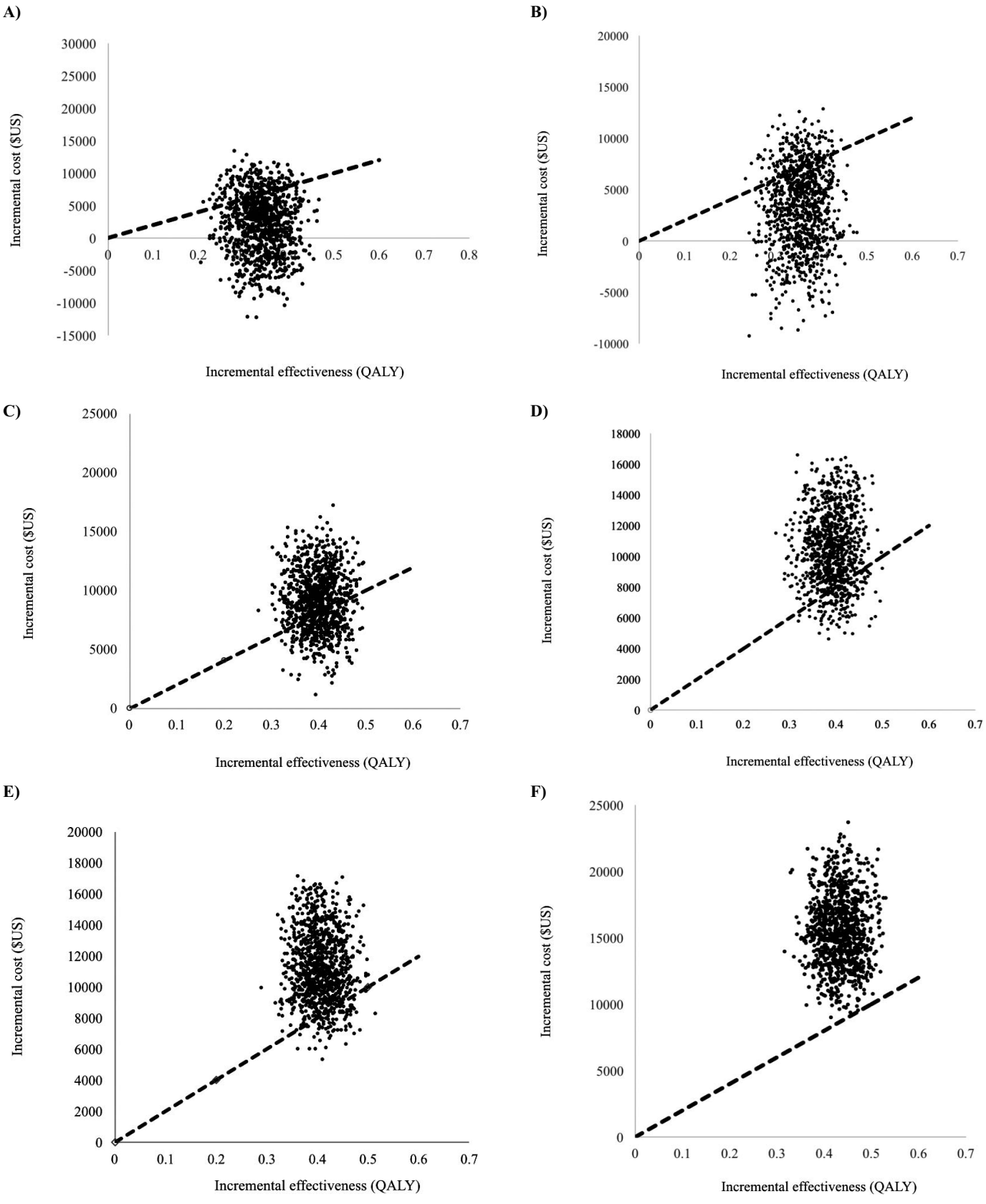

Fig. (4). Simulated results of cost-effectiveness planes by subgroups (**A**) GP1: Women, 50-64 years. Simulated results of cost-effectiveness planes by subgroups (**B**) GP2: Women, 65-74 years. Simulated results of cost-effectiveness planes by subgroups (**C**) GP3: Women, ≥75 years. Simulated results of cost-effectiveness planes by subgroups (**D**) GP4: Men, 50-64 years. Simulated results of cost-effectiveness planes by subgroups (**E**) GP5: Men, 65-74 years. Simulated results of cost-effectiveness planes by subgroups (**F**) GP6: Men, ≥75 years.

Table 4. The probability of being cost-effective given willingness to pay of $20,000.

Mode	%
Average population	48.8
Average population with age-and-gender adjustment	53.3
Specific groups	-
Group 1 (50-64 female)	83.5
Group 2 (65-74 female)	79.2
Group 3 (≥ 75 female)	37.1
Group 4 (50-64 male)	15.2
Group 5 (65-74 male)	7.8
Group 6 (≥ 75 male)	0.2

Phase IIa after 6% of immunized patients developed symptoms of aseptic meningoencephalitis [27]. This might be caused by deleterious auto-toxic T cell response, which is related to the higher risk of APOE ε4 alleles carrier [4, 28]. Previous study supporting this evidence showed that patients with APOE ε4 alleles had higher hazard to develop amyloid-related imaging abnormalities after having passive immunotherapy of bapineuzumab [29]. Other studies showed that there were better responses in subjects with APOE alleles or mild AD after treatment [30, 31] but higher risk of deterioration without disease modifying intervention. There are emerging secondary prevention trials for asymptomatic individuals with positive AD biomarkers. Although there is no primary prevention study now [14], using state-of-the-art biomarkers to differentiate specific subgroups (find the right patients) is the hallmark of the future immunotherapy for AD. Moreover, previous studies of cholinesterase inhibitor treatment have shown different benefits based in different genotypes, such as APOE [32], α7 nicotinic receptor (CHRNA7) [33] polymorphisms and butyrylcholinesterase genotypes [31]. Although there is no study incorporating genetic profiles into the current trials of immunotherapy, this new approach is a promising tool in future.

Current immunotherapy is based on amyloid cascade hypothesis, especially on amyloid β (Aβ). A number of failed clinical trials of immunotherapy implied that immunotherapies targeting Aβ alone may be insufficient and downstream pathologies are independent. Intravenous Immunoglobulin (IVIG) has been proved to protect hippocampal neurons in rats and rescue the dying neurons from oxidative insults [34]. The benefits of IVIG are likely due to anti-inflammatory, decreasing the production of reactive oxygen species (ROS) and increasing levels of synaptic proteins [35]. According to the recent result of the clinical trial [36], the optimized dosage and appropriate subgroups (*e.g.* APOE4 carriers) would play a key role in the treatment efficacy of IVIG [37]. No matter what immunotherapy effective is, current studies have shown that the heterogeneities from biomarkers or genetic polymorphisms would affect the efficacy of treatment. Our study result indirectly implied similar results and provided the model to analyze the heterogeneity of CEA of immunotherapy for AD in future. It is also consistent with Golde *et al.*'s viewpoint: selecting the right drug for the appropriate patient groups at the right time for future clinical trials of immunotherapy for AD [14].

In spite of illustrating the heterogeneity of CEA of vaccination for AD by using our proposed approach, there are still some limitations in our study. The efficacy was estimated from clinical trials of AN1792 in our previous study. Although the clinical trials of AN1792 were suspended early, new second generation active immunotherapy of CAD106 [38, 39] or new technology based on mechanisms of molecular mimicry of AFFITOPE-peptides is underway [40]. Furthermore, the DNA Aβ42 vaccinations may provide safer and more effective removal of amyloid [11]. Similarly, anti-tau immunotherapy has been also emerging although the first generation tau immunotherapy trials are underway [12, 14]. Furthermore, the transition probability and the effect size of covariates were only summarized from CERAD database. Hence, this proposed model should be updated by the latest research in future before extrapolation. In addition, the heterogeneity was only taken by age groups and gender based on the original CERAD study.

CONCLUSION

In conclusion, this study indicated the CEA of vaccination for AD existed huge heterogeneity, which could be presented by Markov regression model. With the development of personalized medicine and evidences of factors affecting efficacy of treatment for AD, we can update the current study and evaluate cost-effectiveness of vaccination for AD in the average level and specific subgroups.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

There were no sources of founding or potential conflicts of interest for either author.

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Declared none.

APPENDIX

The average annual transition rates (λ_{ij}) have been published in previous research [15]. Therefore, transition intensity (average hazard rate) was computed from the transition probability as follows (Equation **1**):

$$p_{ij} = 1 - \exp(\lambda_{ij} t)$$

$$\lambda_{ij} = -\ln(1 - p_{ij})/t, \quad \text{where t=1 due to annual probability}$$

i, j mean from status *i* to status *j*; p_{ij} is the annual transition probability from status *i* to status *j*; λ_{ij} is the average annual transition rate from status *i* to status *j*. Then, the proportional hazard with exponential form was applied as follows (Equation **2**):

$$\lambda_{ij}(t) = \lambda_{ij0}(t) \cdot \exp(\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3) \quad \text{(Eq. 2)}$$

Where X_1 is the gender (male: 1 and female: 0), X_2 and X_3 are the dummy variables for the age groups 65-74 yrs and ≥75yrs; λ_{ij0} is the baseline annual transition rate from status *i* to status *j* and it stands for the subgroup of female with 50-64 years of age. The cohort of CERAD (70.8 ± 0.8 years of age) was composed of 40% male, and 17% were 50-64 years of age, 38% were 65-74 years of age and 45% were 75 or older. When the same percentage of the gender across all age groups were assumed, the percentage of each group can be shown in Appendix Table **1**. Meanwhile, the hazard ratios associated with gender and age for stage-to-stage transitions were also estimated by Cox proportional hazard model in the previous study [1]. Therefore, regression coefficients compared to the group of female 40-64 yrs can be calculated (Appendix Table **2**). We can transform the transition rates of each group to the products of λ_{ij0} according to the hazard ratio and regression coefficients. Then we can sum all of these specific transition rates from all stratifications and then calculate the λ_{ij0} from the relationship between λ_{ij0} and λ_{ij}. Hence, estimated annual transition rate for the 6 specific group based on the gender and age (Equation 2) were shown in the Appendix Table **4**. We took the estimation of transition rate from mild to moderate stage as an illustration as follows:

From mild to moderate stage, the annual transition probability (p_{ij}) was 0.322 (from Table **1** of reference 1). Therefore, the annual average transition rate (λ_{ij}) would be 0.388608 according to Equation 1. From CERAD research, the hazard ratios for male, 65-74 age group and ≥75yrs age group were 1.16, 0.83 and 0.82, respectively (from Table **2** of reference 1). Then, the β_1, β_2 and β_3 and the relationships of transition rates compared to the group of female 40-64 yrs (λ_{ij0}) can be calculated (Appendix Table **3**). After weighting the percentage of the group in CERAD cohort (Appendix Table **1**), the sum of these 6 groups transition rates would be 0.9091 λ_{ij0}, which equals to the annual average transition rate the average transition rate 0.388608 (λ_{ij}). Finally, the baseline annual transition rate from mild to moderate would be 0.4274732.

Appendix Table 1. The percentage of six groups by gender and age in CERAD Cohort.

	40-64 yrs	65-74 yrs	>=75 yrs
Female	0.102	0.228	0.27
Male	0.068	0.152	0.18

Appendix Table 2. Estimated regression coefficient.

	β_1*	β_2*	β_3*	$\beta_1+\beta_2$	$\beta_1+\beta_3$
Value	0.14842	-0.18633	-0.19845	-0.03791	-0.05003

*The regression coefficient = Ln (hazazrd ratio)

Appendix Table 3. The relationship of specific transition rate compared to the female 40-64 years (λ_{ij0}).

	40-64 yrs	65-74 yrs	>=75 yrs
Female	1	0.83	0.82
Male	1.16	0.9628	0.9512

Appendix Table 4. The estimated base-case and age-and-gender specific annual transition rates by transition states.

States	Annual Baseline Transition Rate (λ_{ij0})	Age-and-gender Specific Annual Transition Rates (λ_{ij})
Mild to moderate	0.4274732	0.4274732*exp(0.14842*Gender-0.18633*Age1-0.19845*Age2)
Mild to severe	0.0473162	0.0473162*exp(0.37844*Gender-0.38566*Age1-0.28768*Age2)
Mild to death	0.0060221	0.0060221*exp(0.5766*Gender+0.5822*Age1+1.4061*Age2)
Moderate to severe	0.4304458	0.4304458*exp(0.067659*Gender+0.019803*Age1-0.174353*Age2)
Moderate to death	0.0182164	0.0182164*exp(0.61519*Gender+0.39204*Age1+1.20297*Age2)
Severe to death	0.0993913	0.0993913*exp(0.45742*Gender+0.11333*Age1+0.52473*Age2)

Gender: categorical variable: male=1, female=0
Age1: age group of 65-74 years old; Age 2: age group of ≧ 75 years old

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