Use of GLP-1 receptor agonists and subsequent risk of acute liver injury

A cohort analysis in the OMOP CDM (GLP1-DILI)

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Some Background

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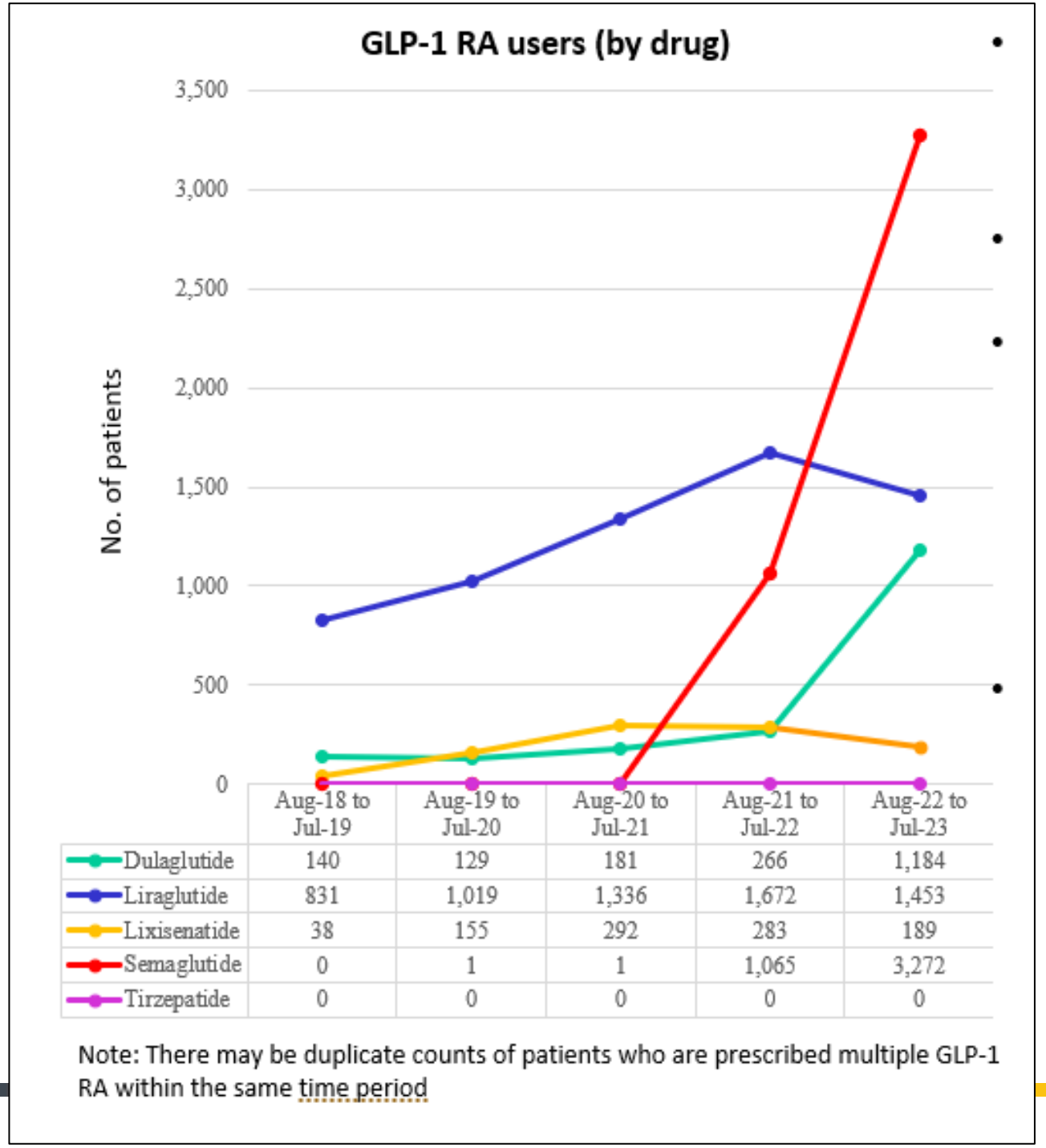
Study Context

- GLP-1 receptor agonists (GLP-1 RA) are increasingly used as treatment for T2DM and obesity.
- Several case reports have arisen on acute liver injury (ALI) post-prescription of GLP-1 RA
- Rising usage and seriousness of ALI warrants closer assessment to evaluate the risk

Clinical context

- GLP-1 receptor agonists (GLP-1 RA) are increasingly used as treatment for T2DM and obesity



	Aug-18 to Jul-19	Aug-19 to Jul-20	Aug-20 to Jul-21	Aug-21 to Jul-22	Aug-22 to Jul-23
Dulaglutide	140	129	181	266	1,184
Liraglutide	831	1,019	1,336	1,672	1,453
Lixisenatide	38	155	292	283	189
Semaglutide	0	1	1	1,065	3,272
Tirzepatide	0	0	0	0	0

Note: There may be duplicate counts of patients who are prescribed multiple GLP-1 RA within the same time period

Acute liver injury safety concerns have appeared

ABSTRACTS: CLINICAL VIGNETTES/CASE REPORTS - LIVER

Drug-induced Liver Injury Associated with the Glucagon-like Peptide 1 (GLP-1) Agonist Liraglutide

1131

Kern, Emily MD; VanWagner, Lisa MD, MS; Rinella, Mary MD, FACG

Author Information

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Article

Liraglutide-Induced Hepatotoxicity

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TIRZEPATIDE-RELATED ACUTE LIVER INJURY

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LIVER: CLINICAL VIGNETTES/CASE REPORTS

S3653 Semaglutide-Induced Hepatotoxicity: A Rare Case of Drug Induced Liver Injury

Galeano Lovera, Santiago F. MD*; Gnanapandithan, Karthik MD, MS

Author Information

The American Journal of Gastroenterology 118(10S):p S2370, October 2023. | *DOI:* 10.14309/01.ajg.0000964252.91007.e2

FREE

Metrics

Introduction:

Semaglutide is a GLP-1 analogue approved for the treatment of type 2 diabetes and weight loss. Drug-induced liver injury (DILI) is a rare but significant cause of liver disease associated with various medications. We present a case of a 67-year-old woman who developed acute hepatocellular injury after initiation of semaglutide therapy for weight loss.

EMA has conducted a study

Methods applied

- IQVIA™ DA Germany database
- New-user, active comparator design
- Diagnosis codes only for ALI
- Propensity score matching
- Intention-to-treat analysis
- Time-to-event, Cox regression

Box 1. Summary of study methods	
	• Those with recorded history of the outcome prior index-date (Excluded conditions are specific to each outcome, see more details in Section 5.3).
Treatment protocols	Initiate any of the following substances at **index-date** (as monotherapy). *Target arms (exposure of interest):* • liraglutide (target arm [Cohort 1], class: GLP-1 receptor agonist) *Comparator arms:* • empagliflozin (comparator arm [Cohort 2], class: SGLT-2 inhibitor) • dapagliflozin (comparator arm [Cohort 3], class: SGLT-2 inhibitor) • sitagliptin (comparator arm [Cohort 4], class: DPP-4 inhibitor)
Assignment procedures	We assumed treatments are randomly assigned conditional on the propensity score (PS) [see Section 5.6, Potential confounding factors]
Index-date (cohort entry, beginning of follow-up)	The index-date was the date of the initiation of treatment defined as a prescription date for liraglutide, empagliflozin, dapagliflozin or sitagliptin.
Outcome	First ever recorded occurrence of any of the conditions (incident event) included in the definition for each outcome: "Diseases of liver" (comparison 1), acute hepatic injury (comparison 2), acute hepatic injury with no chronic hepatic failure (comparison 3) [See section 5.6, Outcomes, and Annex II]
Follow-up	Patients were followed-up from index-date up to maximum of 90 days. Thus, patients were followed-up from index-date to the earliest of: date of first occurrence of outcome, loss to follow-up, death, end of follow-up (90 days) or end of the study period [See Section 5.5, Follow-up period]

Some notable differences between liraglutide and comparator

Table S3. Predefined[1] baseline characteristics before and after PS matching in **T2DM patients** in the IQVIA™ DA Germany database

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	%	%	SMD	%	%	SMD
Age group						
10 - 14		0.0				
15 - 19	0.1	0.0	0.04	0.1	0.1	0.00
20 - 24	0.3	0.1	0.06	0.3	0.3	0.01
25 - 29	0.6	0.2	0.08	0.5	0.7	-0.02
30 - 34	1.4	0.5	0.11	1.4	1.5	0.00
35 - 39	2.9	1.2	0.13	2.5	2.5	0.00
40 - 44	5.3	2.3	0.18	4.3	4.6	-0.02
45 - 49	8.1	4.7	0.15	7.7	7.6	0.01
50 - 54	14.5	9.2	0.17	13.1	14.4	-0.04
55 - 59	17.6	13.8	0.11	17.1	17.3	-0.01
60 - 64	17.0	16.5	0.01	16.5	16.4	0.00
65 - 69	14.3	16.0	-0.05	15.2	15.9	-0.02
70 - 74	9.6	13.9	-0.13	9.8	8.0	0.06
75 - 79	5.4	10.7	-0.18	7.3	6.8	0.02
80 - 84	2.5	7.4	-0.20	3.5	3.2	0.02
85 - 89	0.3	2.9	-0.17	0.5	0.6	-0.01
90 - 94	0.0	0.5	-0.07	0.1	0.0	0.02
95 - 99		0.0			0.1	
Gender: female	45.6	35.8	0.20	47.1	49.5	-0.05
Medical history: General						

Some notable differences between liraglutide and comparator

Table S3. Predefined[(1)] baseline characteristics before and after PS matching in **T2DM patients** in the IQVIA™ DA Germany database

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	**%**	**%**	**SMD**	**%**	**%**	**SMD**
Medical history: Cardiovascular disease						
Atrial fibrillation	2.3	3.4	-0.06	1.9	1.8	0.01
Cerebrovascular disease	3.8	4.9	-0.05	2.9	2.5	0.03
Coronary arteriosclerosis	4.0	8.7	-0.18	4.3	4.0	0.01
Heart disease	21.7	32.0	-0.22	18.8	17.8	0.03
Heart failure	6.5	9.7	-0.11	5.4	5.1	0.01
Ischemic heart disease	10.1	16.1	-0.17	8.7	7.7	0.04
Peripheral vascular disease	9.9	9.2	0.02	7.3	7.3	0.00

Results

No increased ALI risk observed, relative to new users of SGLT2i / DPP4i

Treatment arm	Follow-up (person-years)	n events	IR	95% CI		HR	95% CI	
365 days								
Sitagliptin	7710.90	25	**3.24**	2.07	4.54	**1.00**	[Reference]	
Liraglutide	7760.48	10	**1.29**	0.52	2.19	**0.40**	0.18	0.80
180 days								
Sitagliptin	4007.91	11	**2.74**	1.25	4.49	**1.00**	[Reference]	
Liraglutide	4016.81	7	**1.74**	0.50	3.24	**0.63**	0.23	1.61
90 days								
Sitagliptin	2080.46	5	**2.40**	0.48	4.81	**1.00**	[Reference]	
Liraglutide	2071.77	<5	(*)	(*)	(*)	**0.80**	0.20	3.04

Incretin-Based Drugs and the Risk of Acute Liver Injury Among Patients With Type 2 Diabetes

Richeek Pradhan,[1,2] Hui Yin,[2] Oriana H.Y. Yu,[2,3] and Laurent Azoulay[1,2,4]

Diabetes Care 2022;45:2289–2298 | https://doi.org/10.2337/dc22-0712

OBJECTIVE

To determine whether the use of dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs), separately, is associated with an in
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RESULTS
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RAs were
1.11, 95%
users of both DPP-4 inhibitors (HR 3.22, 95% CI 1.67–6.21) and GLP-1 RAs (HR 3.23, 95% CI 1.44–7.25).

CONCLUSIONS

In this population-based study, DPP-4 inhibitors were associated with an increased risk of acute liver injury compared with SGLT-2 inhibitors in patients with type 2 diabetes. In contrast, an increased risk of acute liver injury was observed only among female GLP-1 RA users.

RESULTS

Compared with SGLT-2 inhibitors, DPP-4 inhibitors were associated with a 53% increased risk of acute liver injury (HR 1.53, 95% CI 1.02–2.30). In contrast, GLP-1 RAs were not associated with an overall increased risk of acute liver injury (HR 1.11, 95% CI 0.57–2.16). However, an increased risk was observed among female users of both DPP-4 inhibitors (HR 3.22, 95% CI 1.67–6.21) and GLP-1 RAs (HR 3.23, 95% CI 1.44–7.25).

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Objective

- Evaluate risk of ALI in T2DM users of GLP-1 RA compared to DPP4

Phenotype Definition

Evelyn Goh | National University of Singapore

Objective

- Evaluate risk of
  - Acute liver injury [outcome]
  - In T2DM users [cohort]
  - of GLP-1 RA [target exposure]
  - compared to DPP4 [comparator]

Standardizing the question makes it possible to standardize the analysis and standardize the evidence

Analytic use case	Type	Structure
Clinical characterization	**Disease Natural History**	Amongst patients who are diagnosed with <insert disease of interest>, what are the patient's characteristics from their medical history?
	Treatment utilization	Amongst patients who have <insert disease of interest>, which treatments were patients exposed to amongst <list of treatments for disease> and in which sequence?
	Outcome incidence	Amongst patients who are new users of <insert drug of interest> among the population with <insert indication of interest>, how many patients experienced <insert outcome of interest> within <time horizon following exposure start>?
Population-level effect estimation	**Safety surveillance**	Does exposure to <insert drug of interest> increase the risk of experiencing <insert an adverse event> within <time horizon following exposure start>, among the population with <insert indication of interest>?
	Comparative effectiveness	Does exposure to <insert drug of interest> have a different risk of experiencing <insert any outcome (safety or benefit) > within <time horizon following exposure start>, relative to <insert comparator treatment>, among the population with <insert indication of interest>?
Patient level prediction	**Disease onset and progression**	For a given patient who is diagnosed with <insert your favorite disease>, what is the probability that they will go on to have <another disease or related complication> within <time horizon from diagnosis>?
	Treatment response	For a given patient who is a new user of <insert drug of interest> for <insert indication of interest>, what is the probability that they will <insert desired effect> in <time window>?
	Treatment safety	For a given patient who is a new user of <insert drug of interest> for <insert indication of interest>, what is the probability that they will experience <insert adverse event> within <time horizon following exposure>?

Framing clinical question into standardized format

Comparative effectiveness	Does exposure to **<insert drug of interest>** have a different risk of experiencing **<insert any outcome (safety or benefit) >** within **<time horizon following exposure start>**, relative to **<insert comparator treatment>**, among the population with **<insert indication of interest>**?

Comparative effectiveness	Does exposure to **GLP-1 receptor agonists** have a different risk of experiencing **acute liver injury** within **time from day after exposure start to exposure end**, relative to **DPP-4 inhibitors**, among the population with **Type 2 diabetes mellitus**?

Target cohort developed for estimation study: GLP-1 receptor agonist

- Entry event: First drug exposure to **GLP-1 receptor agonist**
- Inclusion criteria:
  - >=365 days of prior observation
  - Age >= 18
  - At least 1 condition occurrence of Type 2 Diabetes Mellitus any time prior
  - 0 occurrences of Type 1 Diabetes Mellitus and Secondary Diabetes any time prior
  - Exposure to metformin (>90-day duration or >3 exposures) any time prior
  - No ‘liver or biliary-related conditions’ any time prior
- Cohort exit: No longer have continuous exposure persistence of 60 days between exposure records

Comparator cohort developed for estimation study: DPP-4 inhibitor

- Entry event: First drug exposure to **DPP-4 inhibitor**
- Inclusion criteria:
  - >=365 days of prior observation
  - Age >= 18
  - At least 1 condition occurrence of Type 2 Diabetes Mellitus any time prior
  - 0 occurrences of Type 1 Diabetes Mellitus and Secondary Diabetes any time prior
  - Exposure to metformin (>90-day duration or >3 exposures) any time prior
  - No 'liver or biliary-related conditions' any time prior
- Cohort exit: No longer have continuous exposure persistence of 60 days between exposure records

Outcome cohort developed for estimation study: acute liver injury

- Entry event: All condition occurrences of acute liver injury
  - Defined by OHDSI phenotype library diagnostic codes
- Inclusion criteria:
  - 0 condition occurrences of chronic hepatic failure on the index date
  - 0 occurrences of ‘acute liver injury’ in the 365d prior to the index date
- Cohort exit:
  - Condition end date + 90 days

Study design

- New user comparative cohort study
  - Executed within each data source across distributed network
- Large Scale Propensity Score (LSPS) model 1:1 matching between target (**GLP1RA**) and comparator (**DPP4i**) cohorts
- Hazard Ratio (HR) estimated using Cox proportional hazards model for outcome of interest (**acute liver injury**) during the 'on treatment' time-at-risk'
- 130 negative control outcomes
- Evidence synthesis across network to produce composite HR
  - Bayesian meta-analysis of all sources passing objective diagnostics

Objective diagnostics

- Empirical equipoise
  - What proportion of target population is close to treatment indifference?
  - **PASS** if Equipoise (Preference score 0.3-0.7) > 0.20
- Covariate balance
  - Are baseline characteristics balanced?
  - **PASS** if Maximum Absolute Standardized Difference of Means after adjustment (Max ASDM) < 0.1
- Residual bias
  - Is the residual bias observed from negative controls small enough to accept that calibrated effect estimates can be trusted as unbiased?
  - **PASS** if Expected Absolute Systematic Error (EASE) < 0.25

Study implementation

- R analysis package is publicly available on Git: https://github.com/ohdsi-studies/Glp1Dili/
  - Uses HADES packages, including Strategus orchestration using CohortGenerator, Characterization, CohortIncidence, CohortMethod, and EvidenceSynthesis packages
- Preliminary results available for exploration using R Shiny:

  https://results.ohdsi.org/app/24_Glp1Dili
  - Uses R Shiny with OhdsiShinyModules

Preliminary results

Incidence: GLP-1 cohort

Source name	Country	Persons at risk	Average Time-at-risk (days/person)	Outcomes	Incidence rate (per 100 person-years)
France Disease Analyzer	France	807	87	0	
Yonsei University Severance CDM	Korea	1,096	51	<5	
Japan Medical Data Center (JMDC)	Japan	4,748	325	<5	
Taipei Medical University	Taiwan	1,380	362	<5	
LPD Australia	Australia	8	35	0	
MarketScan Multi-State Medicaid	U.S.	32,052	279	49	0.20
MarketScan Medicare Supplemental (MDCR)	U.S.	17,690	274	32	0.24
MarketScan Commercial Claims (CCAE)	U.S.	155,857	333	127	0.09
Optum EHR	U.S.	252,236	200	244	0.18
HealthVerity CC	U.S.	726,052	310	1,099	0.18
Iqvia LRx-US9-LAAD	U.S.	2,805,992	340	1,738	0.07
US Department of Veterans Affairs (VA)	U.S.	96,854	479	101	0.08
PharMetrics	U.S.	336,935	327	333	0.11
OPTUM Extended DOD	U.S.	166,471	293	265	0.20

Cohort counts from estimation analyses

Database	Country	Target (GLP1)	Comparator (DPP4)	Matched (per group)
France Disease Analyzer	France	1,861	2,283	621
Yonsei University Severance CDM	Korea	2,400	5,596	571
Japan Medical Data Center	Japan	5,787	13,200	3,134
Taipei Medical University CRD	Taiwan	1,390	6,550	938
MarketScan Multi-State Medicaid	U.S.	32,073	14,191	11,039
MarketScan Medicare Supplemental (MDCR)	U.S.	18,522	8,549	5,924
MarketScan Commercial Claims (CCAE)	U.S.	155,904	47,493	41,273
Optum EHR	U.S.	252,117	134,643	94,372
Healthverity CC	U.S.	726,291	314,846	245,191
Iqvia LRx-US-9-LAAD	U.S.	2,805,776	1,151,914	929,511
US Department of Veterans Affairs (VA)	U.S.	96,869	98,605	32,310
Pharmetrics	U.S.	336,826	111,118	94,143

How many passed diagnostics?

9 have passed so far

Database	OVERALL	COVARIATE BALANCE	EMPIRICAL EQUIPOISE	RESIDUAL BIAS (EASE)
France Disease Analyzer	Fail ❌	FAIL ❌	PASS ✅	FAIL ❌
Healthverity CC	Pass ✅	PASS ✅	PASS ✅	PASS ✅
MarketScan Commercial Claims (CCAE)	Pass ✅	PASS ✅	PASS ✅	PASS ✅
MarketScan Multi-State Medicaid	Pass ✅	PASS ✅	PASS ✅	PASS ✅
MarketScan Medicare Supplemental (MDCR)	Pass ✅	PASS ✅	PASS ✅	PASS ✅
Japan Medical Data Center	Pass ✅	PASS ✅	PASS ✅	PASS ✅
LPD Australia	Fail ❌	FAIL ❌	PASS ✅	NOT EVALUATED
Iqvia LRx-US-9-LAAD	Pass ✅	PASS ✅	PASS ✅	PASS ✅
Optum EHR	Pass ✅	PASS ✅	PASS ✅	PASS ✅
PharMetrics	Pass ✅	PASS ✅	PASS ✅	PASS ✅
Yonsei University Severance CDM	Fail ❌	FAIL ❌	PASS ✅	FAIL ❌
Taipei Medical University CRD	Fail ❌	FAIL ❌	PASS ✅	PASS ✅
US Department of Veterans Affairs (VA)	Pass ✅	PASS ✅	PASS ✅	PASS ✅

Total cohort counts (for this current study)

- Total GLP1 = 4,430,165
- Total DPP4 = 1,894,559
- Total matched = **1,456,897**

Total cohort counts (for this current study)

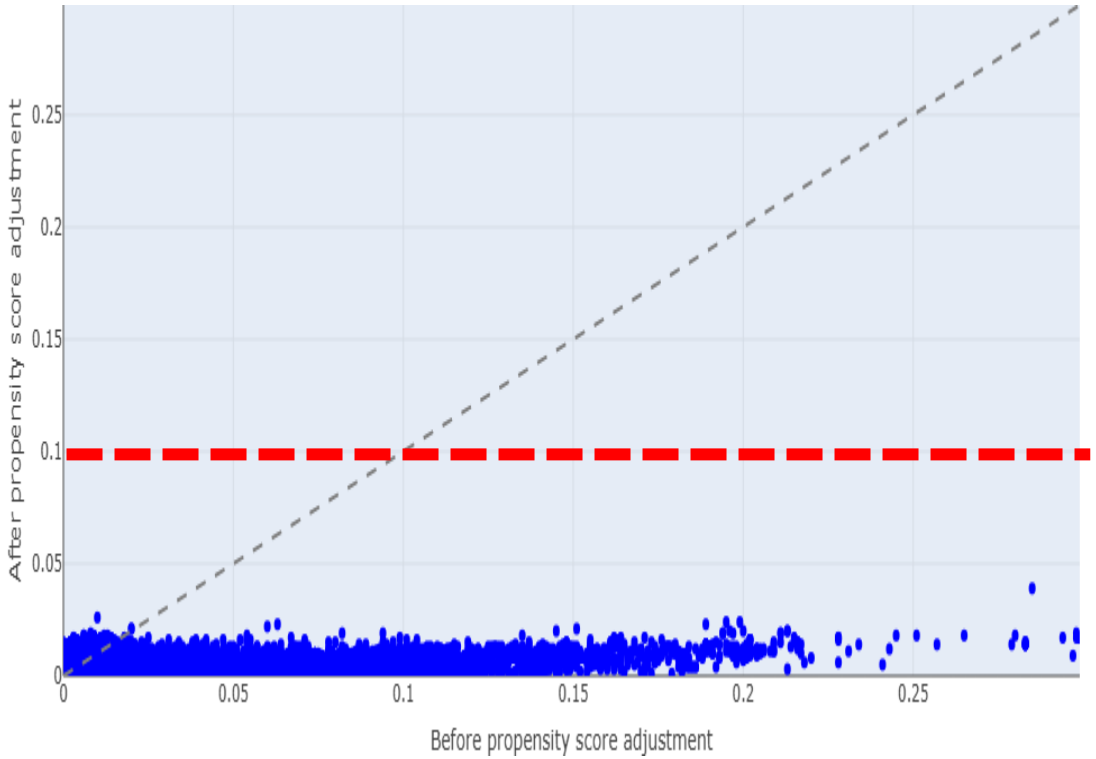
- Total GLP1 = 4,430,165
- Total DPP4 = 1,894,559
- Total matched = **1,456,897**

- Countries: U.S. + Japan

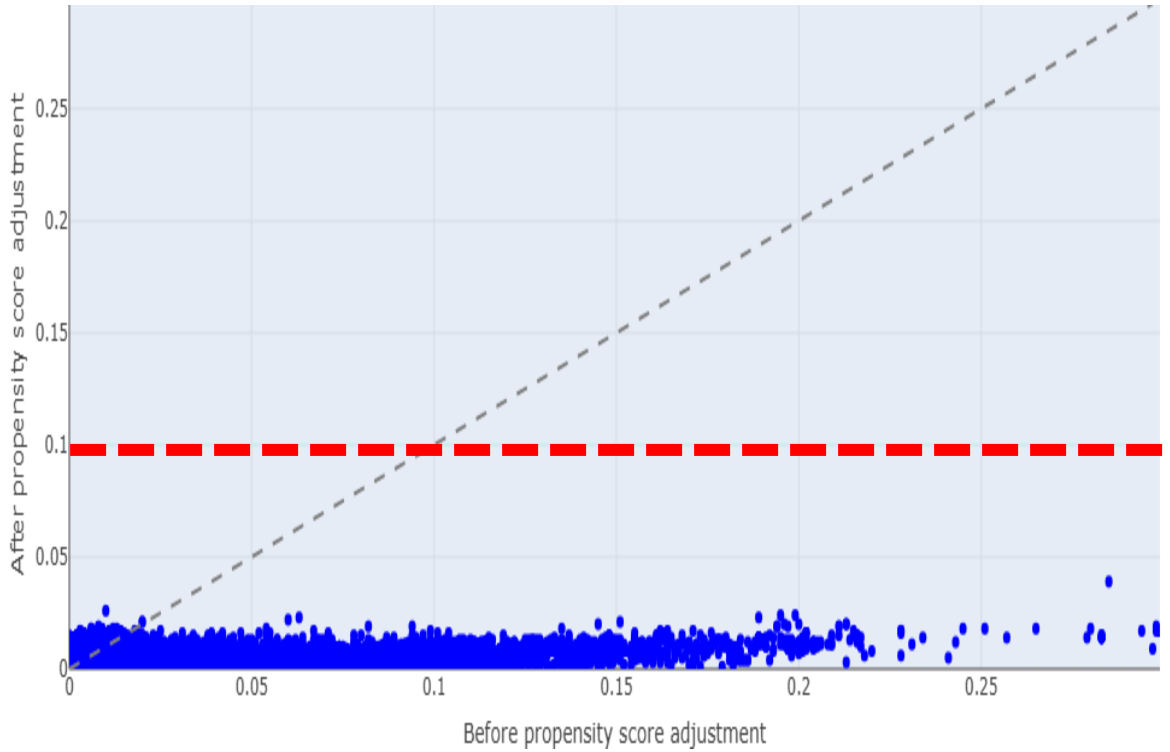
Covariate balance – example databases

- Did our PS matching balance covariates? YES

OPTUM EHR (US)

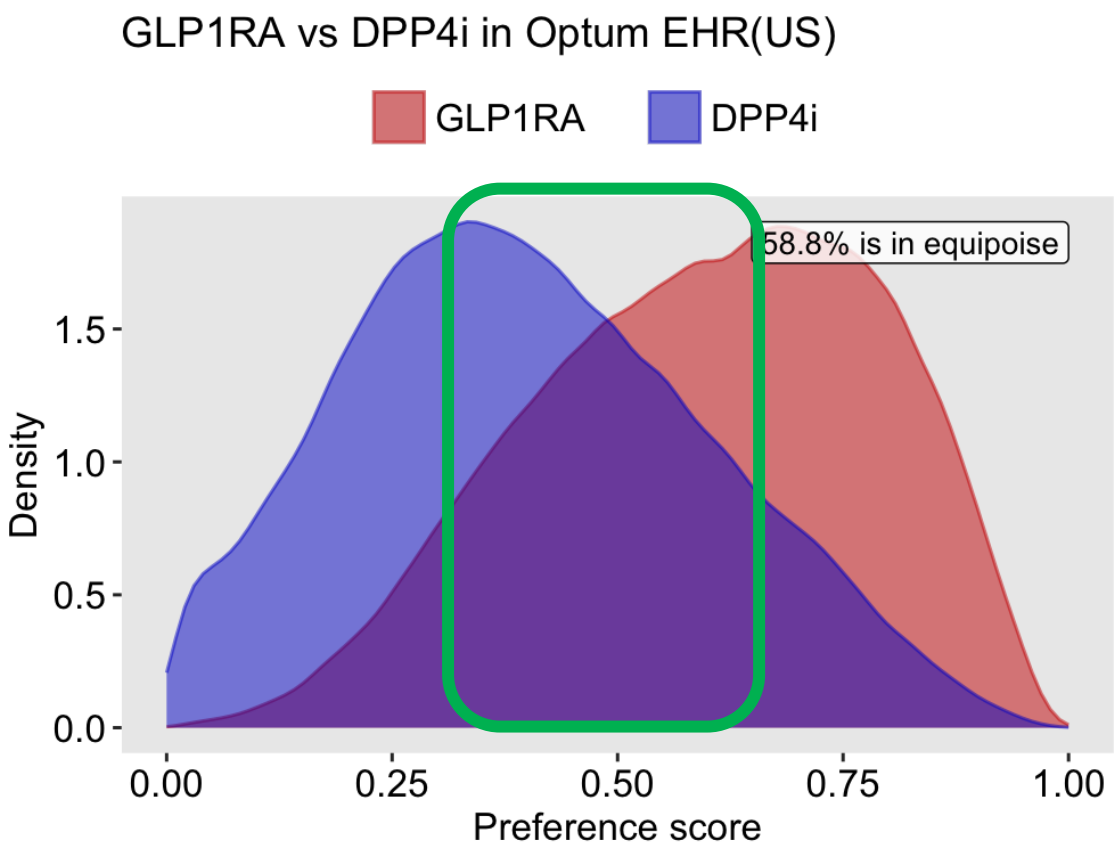


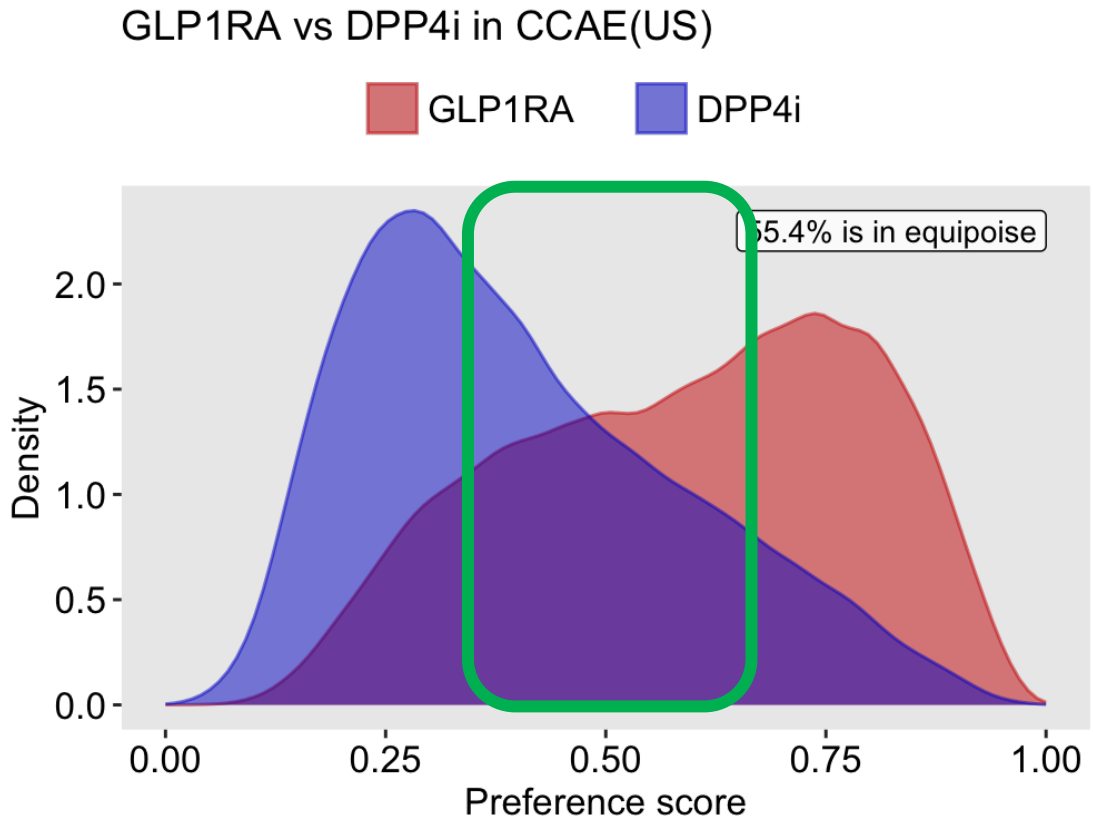
CCAE (US)



Preference score distribution

- Did we have appropriate overlap in preference score? YES





Residual error?

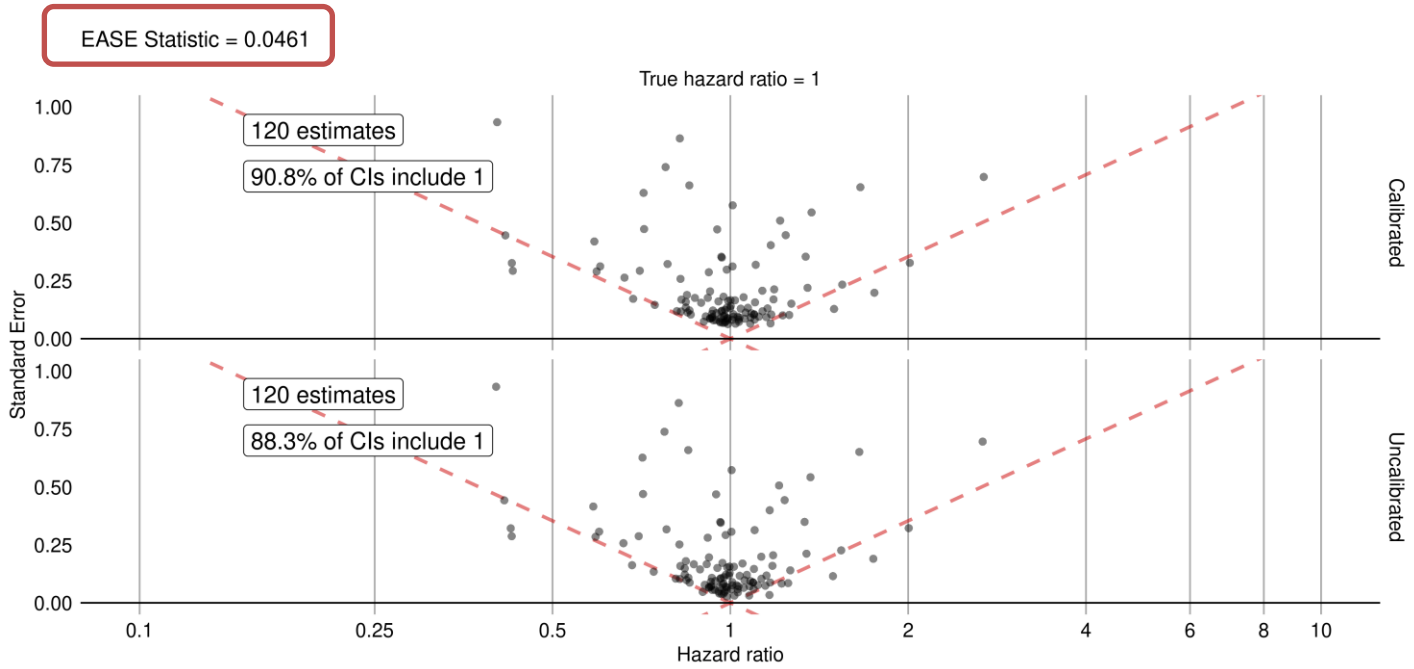
- Can estimate systematic error by using **negative control experiments**:
  - Compare results against ‘known truth’; outcomes unlikely to be associated with GLP-1 use
- Measure Expected Absolute Systematic Error (EASE)

Residual bias

- Did we have assessment and mitigation of residual bias?

- 130 negative controls in total
- Estimates below the line in graphs are statistically different from the true effect size
- Negative control outcomes should return estimate of 1
- 88.3% of negative control estimates had HR with CI that included 1 (before calibration)
- Sufficiently low systematic error; EASE score close to 0 = good calibration

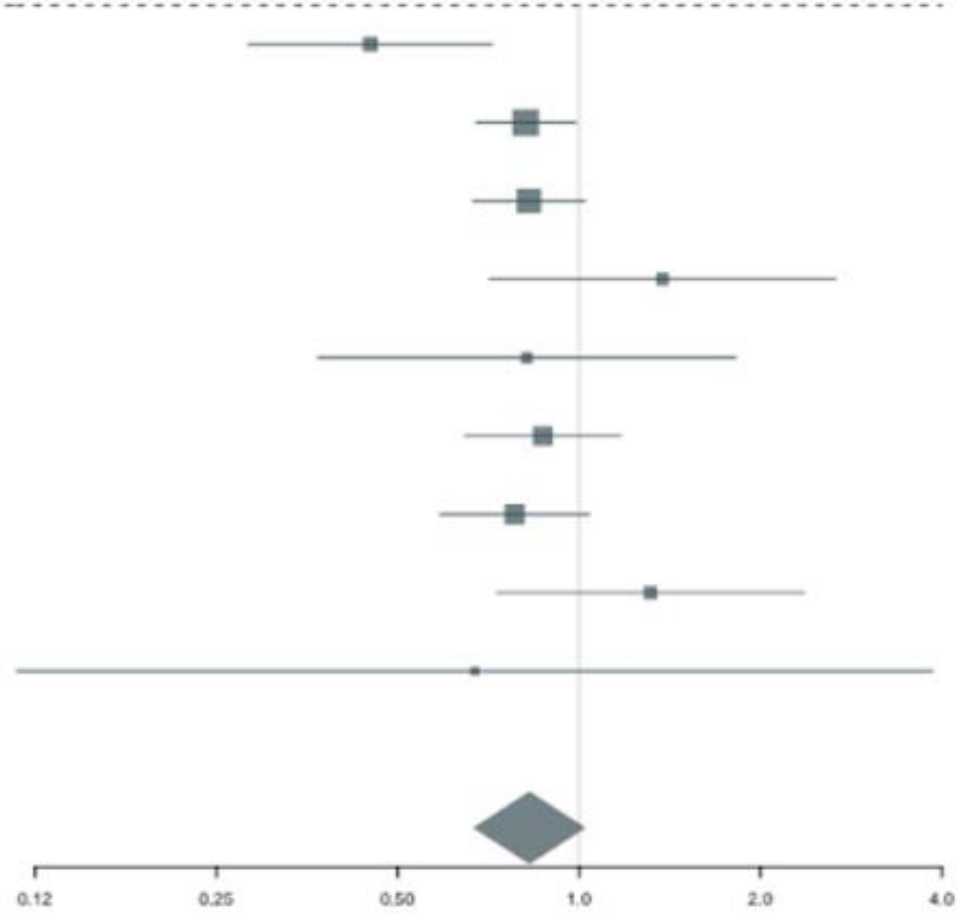
GLP-1 VS DPP-4i (OPTUM EHR)



Meta analysis results

GLP1RA vs DPP4i

Source	Event Rate GLP1RA	Event Rate DPP4i	Hazard ratio (95% CI)
CCAE(US)	0.70	1.48	0.45(0.28–0.72)
HVCC(US)	1.96	2.44	0.82(0.67–0.99)
LAAD(US)	0.78	0.97	0.83(0.67–1.02)
MDCD(US)	2.61	1.83	1.38(0.71–2.67)
MDCR(US)	2.37	3.17	0.82(0.37–1.82)
Optum EHR(US)	1.95	2.26	0.87(0.65–1.17)
PharMetrics(US)	1.11	1.42	0.78(0.59–1.04)
VA(US)	0.94	0.67	1.31(0.73–2.36)
JMDC(JP)	<1.80	1.05	0.67(0.12–3.86)
Meta–analysis	**<1.05**	**1.31**	**0.83(0.67–1.02)**



Summary

- Hypothesis
  - Does exposure to **GLP-1 receptor agonists** have a different risk of experiencing **acute liver injury** within **time from day after exposure start to exposure end**, relative to **DPP-4 inhibitors**, among the population with **Type 2 diabetes mellitus**?

Summary

- Does exposure to **GLP-1 receptor agonists** have a different risk of experiencing **acute liver injury** within **time from day after exposure start to exposure end**, relative to **DPP-4 inhibitors**, among the population with **Type 2 diabetes mellitus**?

- **No evidence** of difference in risk

Summary

- Does exposure to **GLP-1 receptor agonists** have a different risk of experiencing **acute liver injury** within **time from day after exposure start to exposure end**, relative to **DPP-4 inhibitors**, among the population with **Type 2 diabetes mellitus**?

- **No evidence** of difference in risk
- For those who are worried, **reassuring** evidence

Next Steps

Next: Potential future areas of research

- Comparator: SGLT2
- Secondary outcomes

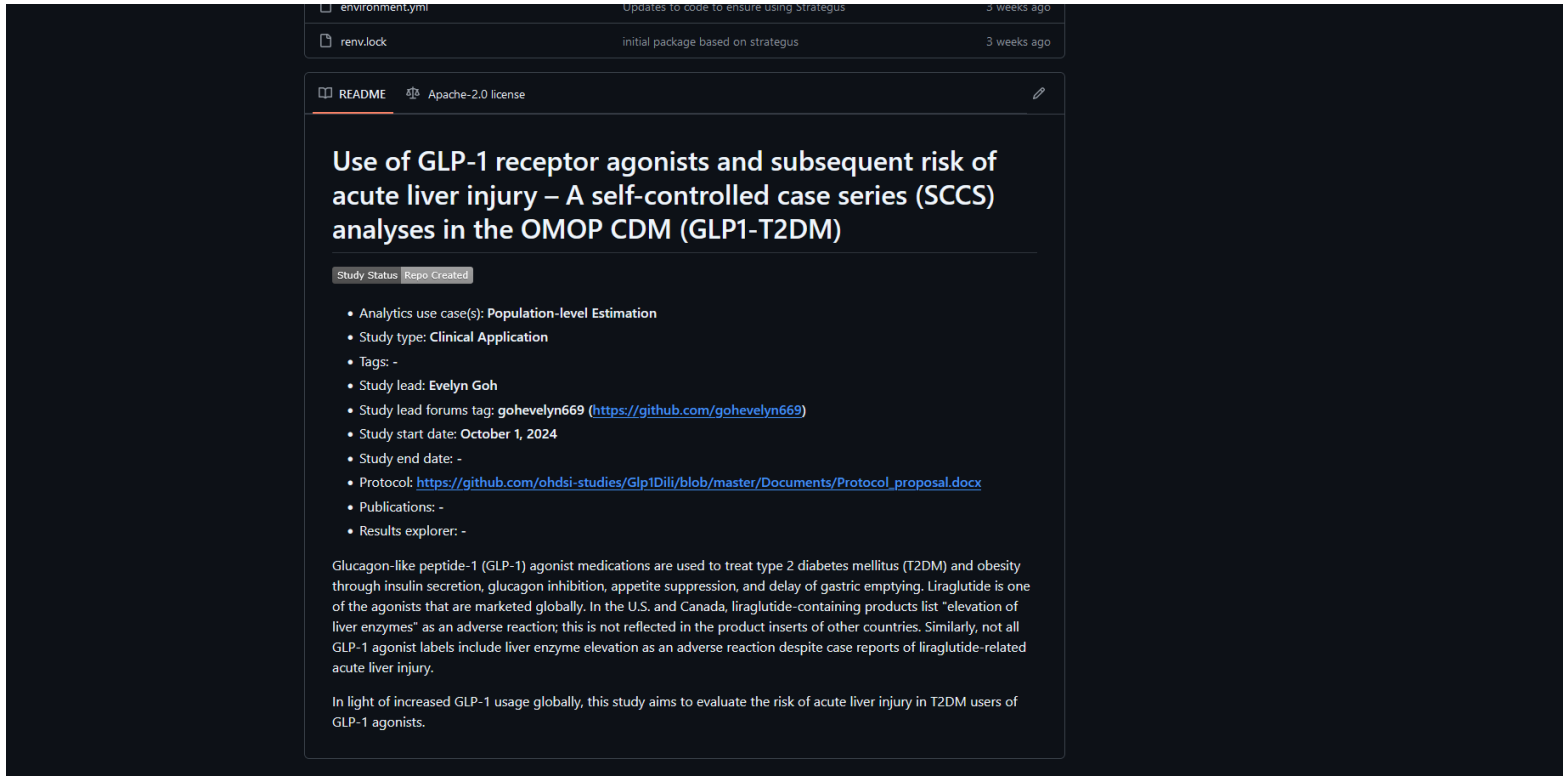
1. Elevated ALT, ALP, and/or bilirubin liver enzymes
   - Any one of the following lab test combinations:
     - ≥ 5 x upper limit of normal (ULN = 41 U/L) alanine aminotransferase (ALT)
     - ≥ 2 x ULN (ULN = 130 U/L) alkaline phosphatase (ALP)
     - ≥ 3 x ULN ALT (ULN = 41 U/L) **and** >2 x ULN bilirubin (ULN = 24 µmol/L)
   - At least 1 confirmation of normal liver enzyme during the 90 days prior to index date.
   - At least 90 days of observation period

2. Cholelithiasis and/or cholecystitis by diagnostic code

Next: Potential future areas of research

- Comparator: SGLT2
- Secondary outcomes
- SCCS
- Subpopulation analysis
- More databases

Next: Running the Package



Next: Atlas and ShinyApp

ATLAS: http://34.148.35.102/#/home

ShinyApp

Next: Additional Data Sources

- U.S. - Optum DoD
- Singapore – Khoo Teck Phuat Hospital

Next: Recruitment

- Recruitment
  - Email: e0983111@u.nus.edu

- Especially!!! Asia!!! Please!!!

Acknowledgements

Thank you very much!

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