Evidence Base Medicine

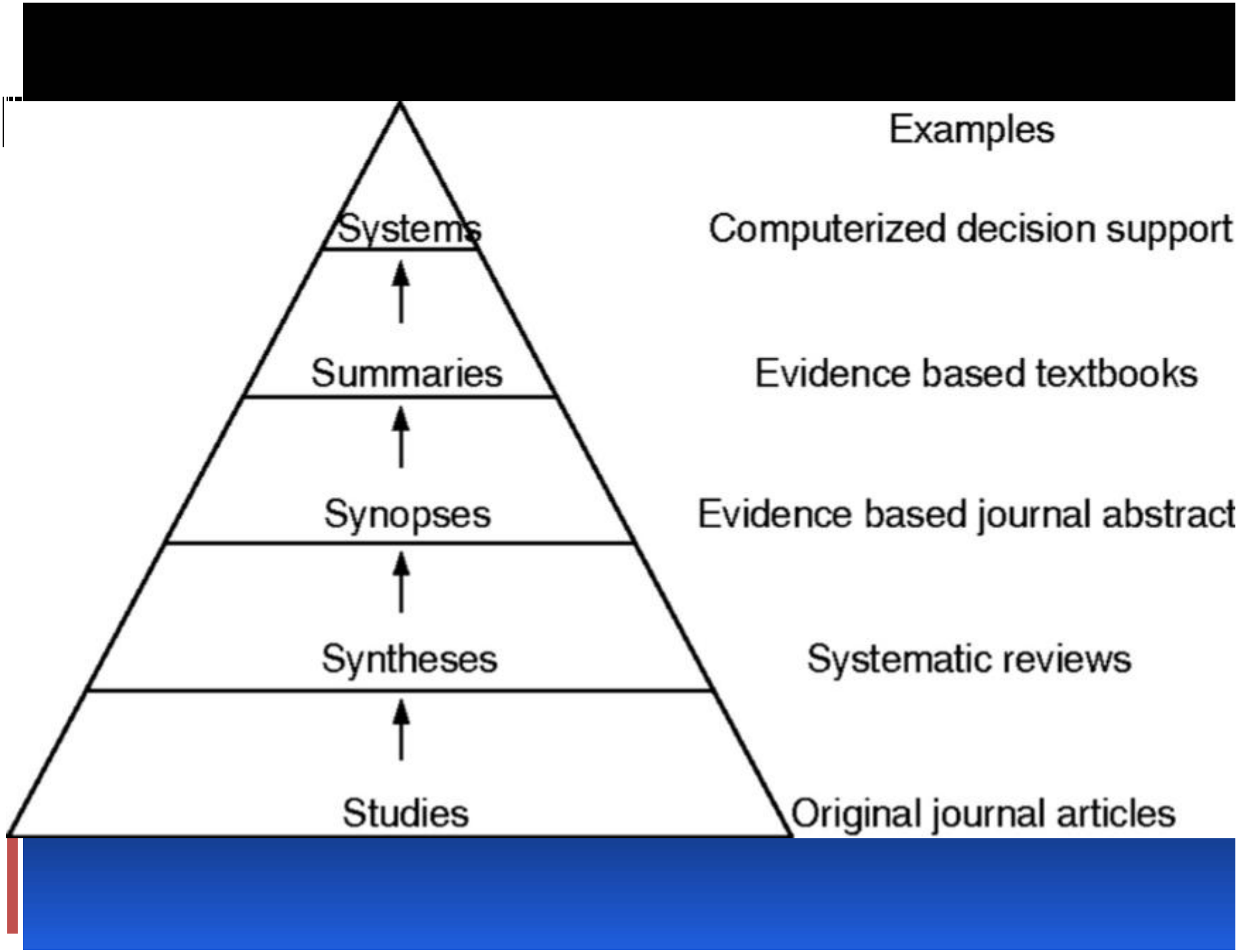
INSTRUCTOR VS 吳宜珍醫師
PRESENTED BY R3林子傑醫師
101.10.09

臨床場景(Clinical scenario)分析

- Liver Cirrhosis 的病人, 一旦發現有Varices後, 要如何選擇治療方式來做bleeding的預防 (primaryPrevention)?
- 藥物 (Non-selective B blocker
- Invasive therapy (Endoscopic ligation !?)
- 何種方式病人比較容易接受!?

P Patient/Problem	LC Varices of patient without previous bleeding
I Intervention	Panendoscopy ligation
C Comparison	Non-selective B blocker
O Outcome	Variceal bleeding rate

搜尋最有用的資料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Banding ligation versus beta-blockers for **primary prevention** ...

... beta-blockers for **primary prevention** in oesophageal varices were ... reduced upper gastrointestinal **bleeding** and **variceal bleeding** compared with non ...

summaries.cochrane.org/CD00454...-oesophageal-varices-in-adults

Beta-blocker plus nitrates for secondary **prevention** of ...

... **prevention** of **variceal bleeding**. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD006709. DOI: 10.1002/14651858.CD006709. More like this. ...

THE COCHRANE COLLABORATION®

Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults (Review)

Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: New, published in Issue 8, 2012.
Review content assessed as up-to-date: 6 February 2012.

Citation: Gluud LL, Krag A. Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 8. Art. No.: CD004544. DOI: 10.1002/14651858.CD004544.pub2.

Main results

Nineteen randomised trials on banding ligation versus non-selective beta-blockers for primary prevention in oesophageal varices were included. Most trials specified that only patients with large or high-risk oesophageal varices were included. Bias control was unclear in most trials. In total, 176 of 731 (24%) of the patients randomised to banding ligation and 177 of 773 (23%) of patients randomised to non-selective beta-blockers died. The difference was not statistically significant in a random-effects meta-analysis (RR 1.09; 95% CI 0.92 to 1.30; I^2 = 0%). There was no evidence of bias or small study effects in regression analysis (Egger's test P = 0.997). Trial sequential analysis showed that the heterogeneity-adjusted low-bias trial relative risk estimate required an information size of 3211 patients, that none of the interventions showed superiority, and that the limits of futility have not been reached. When all trials were included, banding ligation reduced upper gastrointestinal bleeding and variceal bleeding compared with non-selective beta-blockers (RR 0.69; 95% CI 0.52 to 0.91; I^2 = 19% and RR 0.67; 95% CI 0.46 to 0.98; I^2 = 31% respectively). The beneficial effect of banding ligation on bleeding was not confirmed in subgroup analyses of trials with adequate randomisation or full paper articles. Bleeding-related mortality was not different in the two intervention arms (29/567 (5.1%) versus 37/585 (6.3%); RR 0.85; 95% CI 0.53 to 1.39; I^2 = 0%). Both interventions were associated with adverse events.

Next step

- Band ligation > B-blocker in reduction of variceal bleeding
- Mortality !?
- Side effect !?

Original Article

Variceal band ligation versus beta-blockers for primary prevention of variceal bleeding: a meta-analysis

Dhiraj Tripathi[a], Catriona Graham[b] and Peter C. Hayes[a]

European Journal of Gastroenterology & Hepatology 2007, **19**:835–845

Keywords: cirrhosis, ligation, liver disease, meta-analysis

[a]Department of Hepatology, Royal Infirmary of Edinburgh and [b]Epidemiology and Statistics Core, Wellcome Trust Clinical Research Facility, Western General Hospital, Edinburgh, UK

Key word: primary prophylaxis, Variceal bleeding, meta-analysis

Selection criteria

- Study Design: RCT, full publication
- Intervention: ligation and non-selective b-blocker
- Population: EV, secondary portal hypertension
- 9 RCTs out of 185 references
- A total of 734 patients
  - 356 patients in the VBL and 378 in the BB arm
  - The size of each trial ranged from 31 to 152 patients

Exclusion criteria

- (i) different patient population or interventions (n=109)
- reference being a review article (n=38)
- (iii) reference being not an RCT (n=13)
- (iv) reference being an editorial (n=8)
- (v) reference being a letter (n=8).

Table 1 Clinical characteristics at recruitment

Author, (year of publication)	Recruiting centres (*n*)	Patients (*n*)	ALD (%)	Childs's class (% A/B/C)	Mean age (years)	Male (%)	Grade of oesophageal varices (%)	Red signs (%)	Gastric varices (%)	HVPG (mmHg)
Variceal band ligation/β-blockers										
Sarin (1999) [20]	1	45/44	27/41	(16/51/33)/ (20/50/30)	44/39	73/73	III (71/77), IV (29/23)	n.a.	18/20	n.a.
De (1999) [19]	1	15/15	14/20	(33/53/14)/ (40/47/13)	42/39	67/80	III (13/27), IV (87/73)	n.a.	n.a.	16/15
Lui (2002) [21]	6	44/66	73/62	(31/36/33)/ (27/38/35)	54/55	61/53	II (91/82), III (9/18)	0/6	5/5	n.a.
Lo (2004) [22]	1	50/50	20/20	(44/42/14)/ (48/34/18)	55/57	74/80	F2 (58/64), F3 (42/36)	34/34	12/36	n.a.
Schepke (2004) [23]	27[a]	75/77	53/49	(45/41/14)/ (48/40/12)	54/57	67/70	II (43/46), III (57/54)	39/39	13/13	n.a.
Jutabha (2005) [7]	3	31/31	13/10	(39/39/22)/ (26/48/26)	54/55	68/74	3–5 mm varices + red signs (3/10), >5 mm varices (97/90)	For >5 mm varices (81/62)	18/13	n.a.
Thuluvath (2005) [9]	1	16/15	31/7	(35/45/20)	50/54	62/47	F2/F3 varices in all – no further details	n.a.	Full data unavailable	18/21
Psilopoulos (2005) [8]	1	30/30	27/23	(43/40/17)/ (50/40/10)	62/59	73/67	II (77/77), III (23/23)	100/100	0/0	n.a.
Lay (2006) [10]	1	50/50	20/22	(44/42/14)/ (46/36/18)	56/55	76/80	F2/F3 varices in all	[b]	0/0	n.a.

ALD, alcoholic liver disease; HVPG, hepatic venous pressure gradient; n.a., not available.

[a]Ten centres enrolled ≥ 6 patients.

[b]All patients had at least one of the following: red whale markings, cherry-red spot, haematocystic spot.

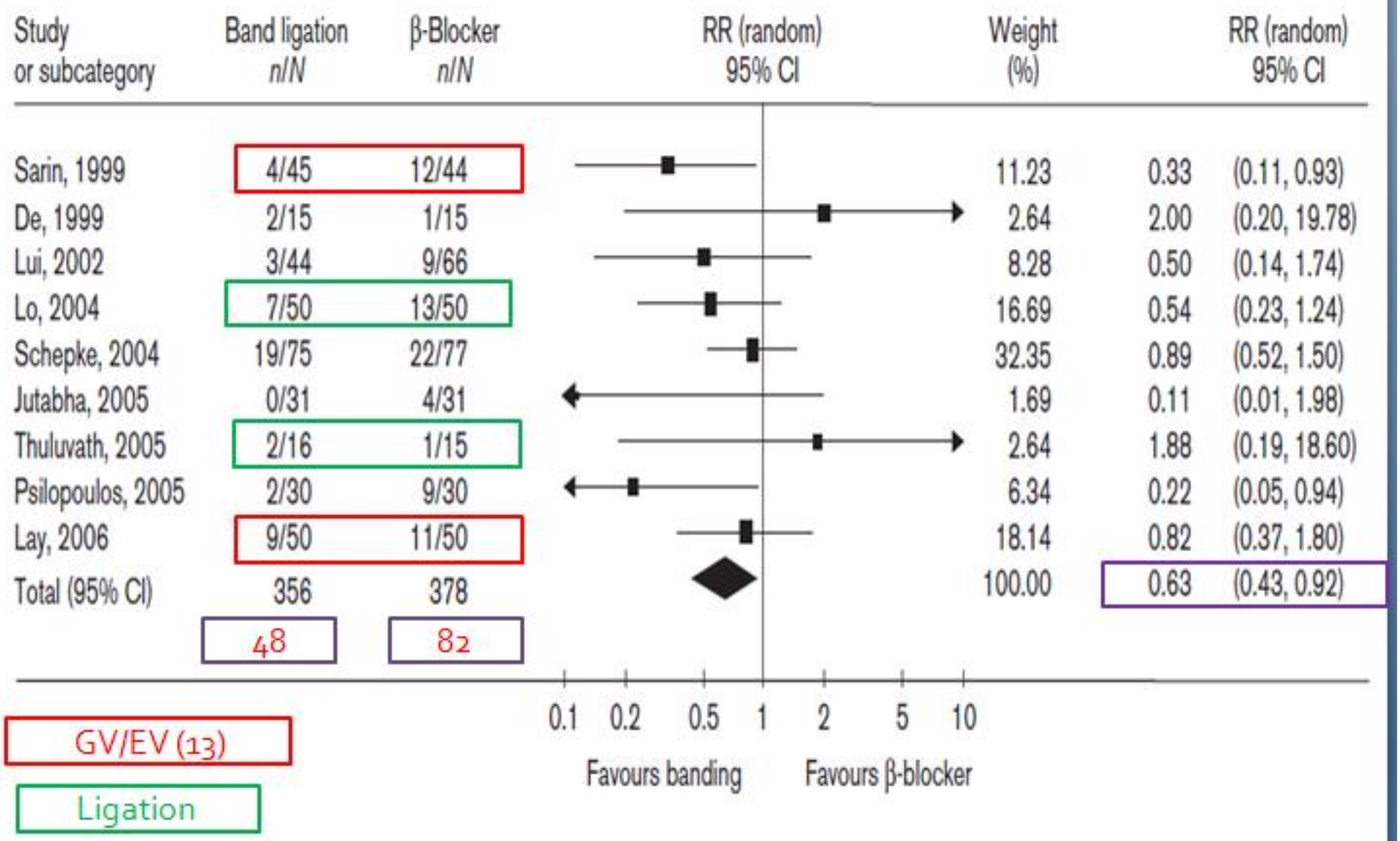
Table 3 Quality assessment of trials

Author	Randomization list generated	Concealment of treatment allocation	Outcome assessment	Intention-to-treat analysis	Completeness of follow-up (VBL/BB, %)
Sarin *et al.* [20]	Table of random numbers	NR	Unblinded	Yes	100/100
De *et al.* [19]	NR	NR	Unblinded	Yes	NR
Lui *et al.* [21]	Randomization in batches of 18 patients	Sealed opaque envelope	Unblinded	Yes	95/92
Lo *et al.* [22]	Table of random numbers	Sealed opaque envelope	Unblinded	Yes	96/100
Schepke *et al.* [23]	Randomization centrally in blocks of six patients per center	Central randomization	Unblinded	Yes	100/100
Jutabha *et al.* [7]	Randomization centrally in blocks of four patients per center	Sealed opaque envelope	Unblinded	Yes	100/100
Thuluvath *et al.* [9]	NR	Sealed envelope	Unblinded	Yes	100/100
Psilopoulos *et al.* [8]	Table of random numbers	NR	Unblinded	Yes	100/100
Lay *et al.* [10]	NR	Sealed envelope	Unblinded	Yes	96/94

BB, β-blocker; NR, not reported; VBL, variceal band ligation.

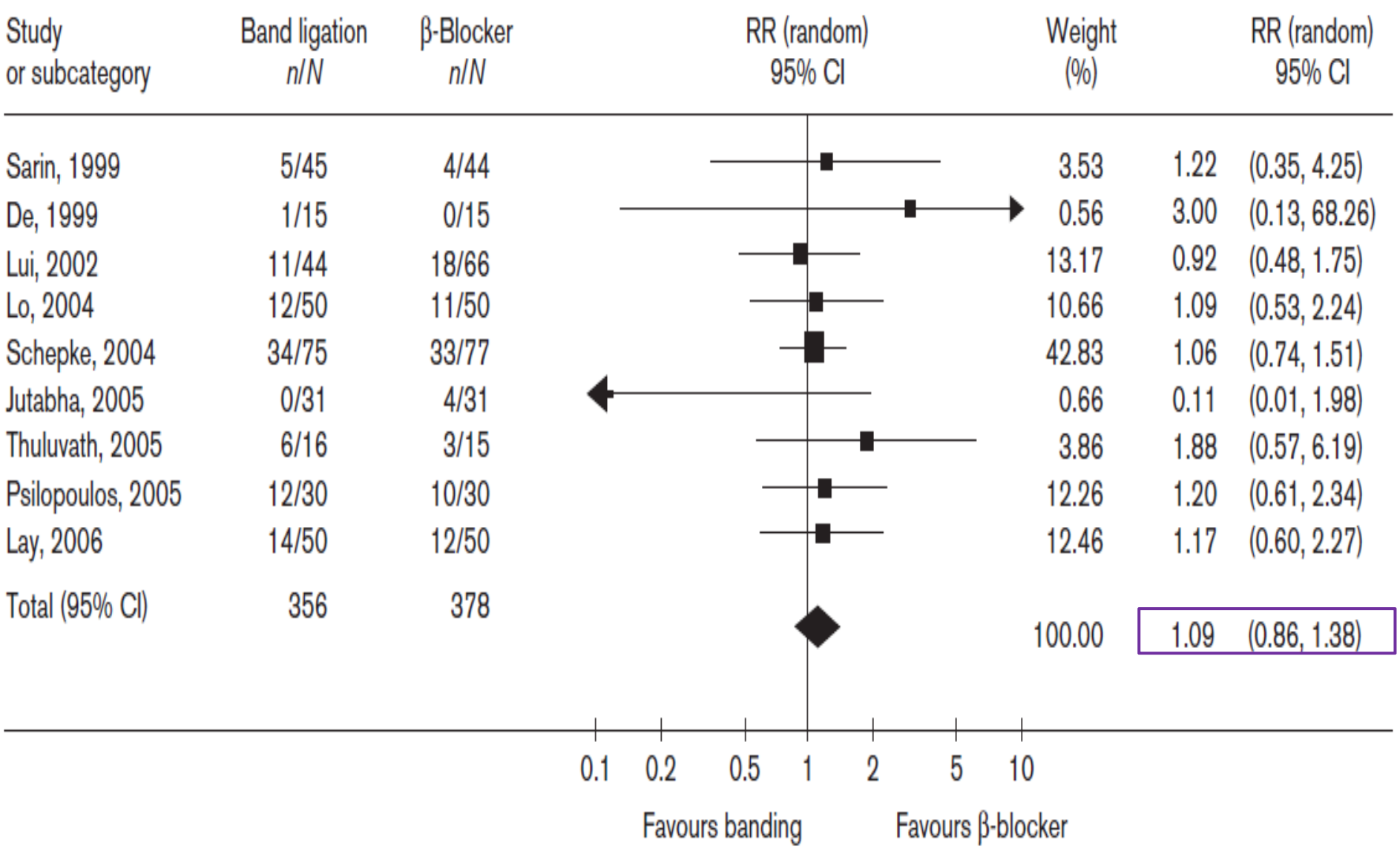
Result

Fig. 1



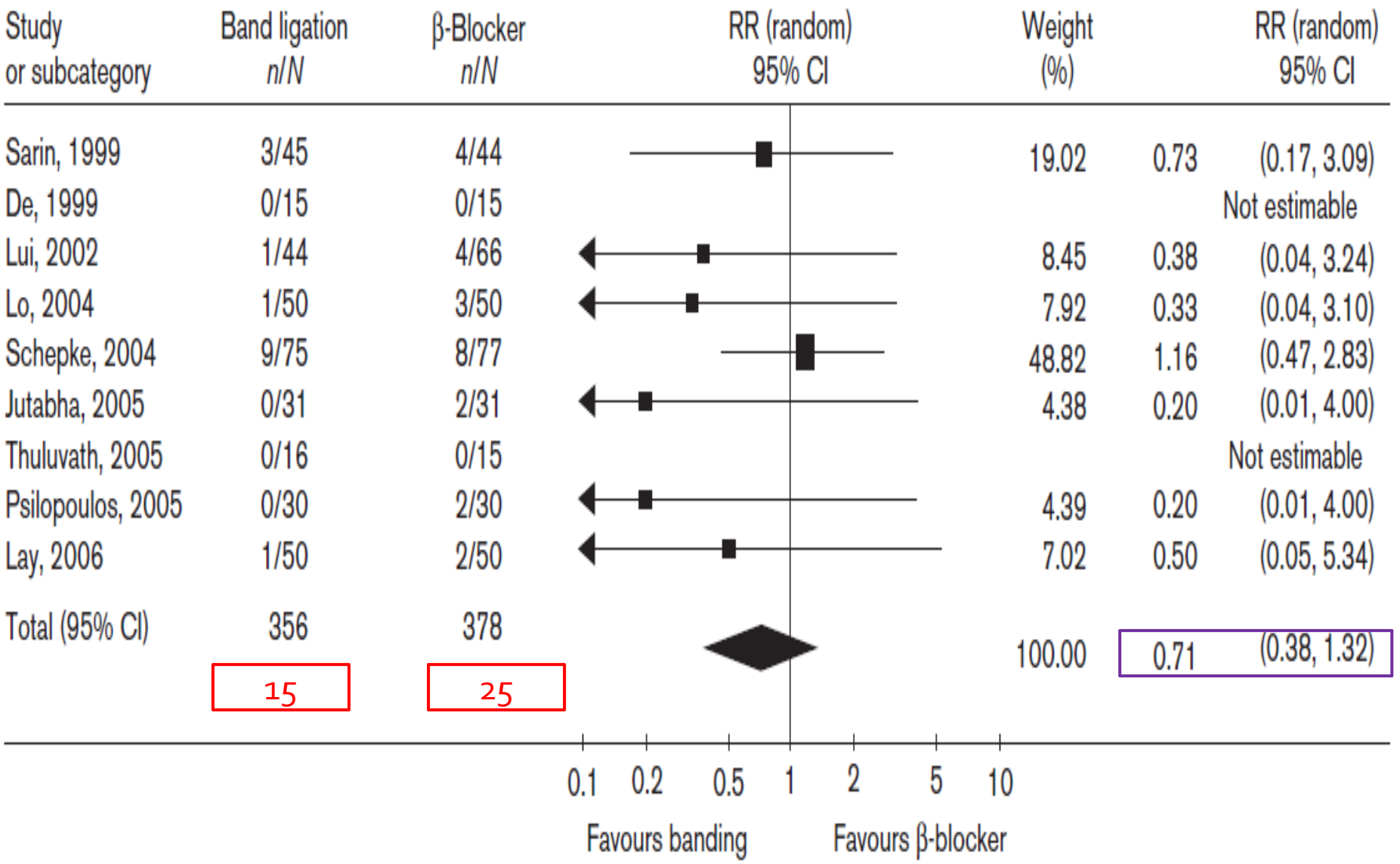
Forest plot for first variceal bleed. CI, confidence interval; RR, relative risk.

Fig. 2



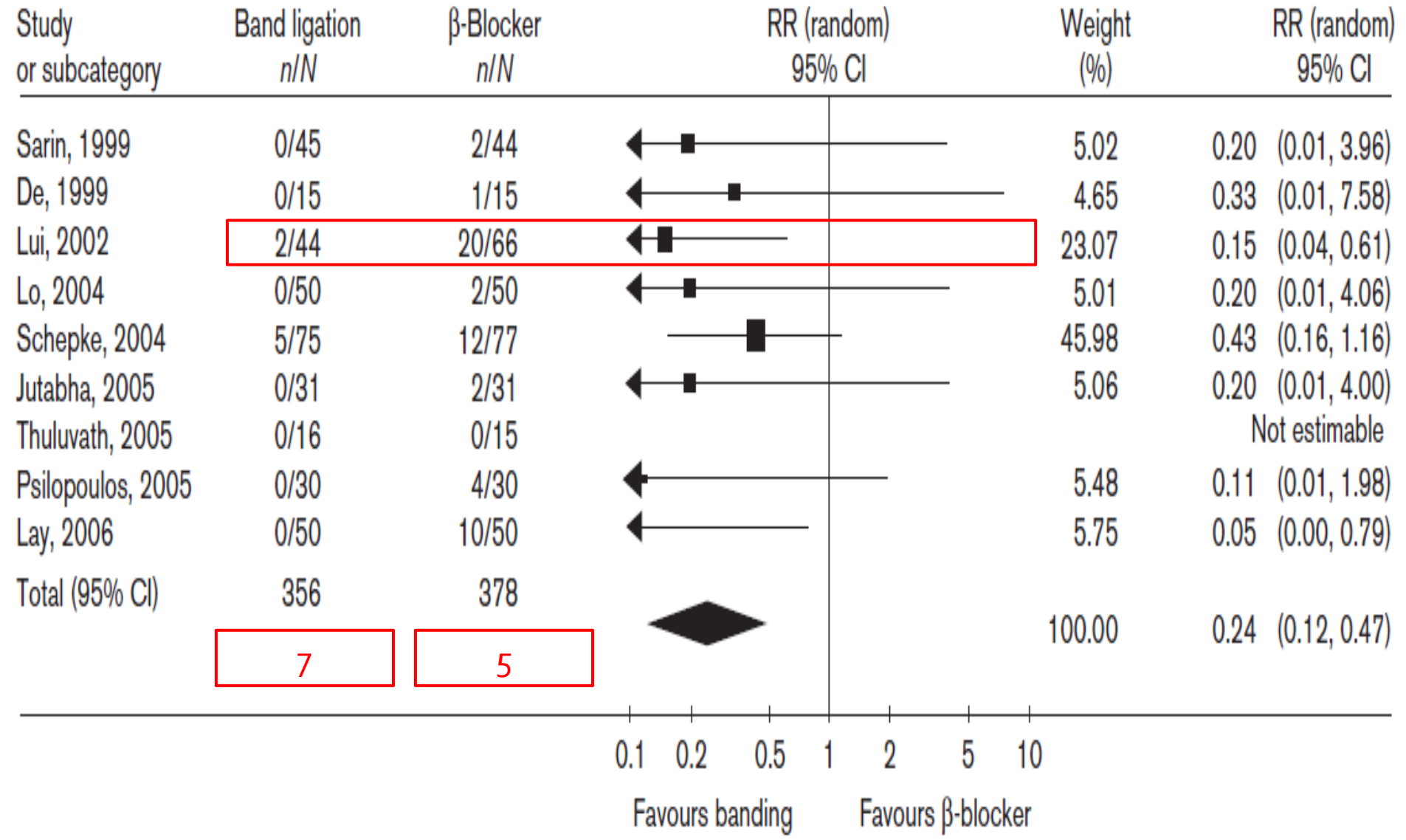
Forest plot for overall mortality. CI, confidence interval; RR, relative risk.

Fig. 3



Forest plot for bleed-related mortality. CI, confidence interval; RR, relative risk.

Fig. 4



Forest plot for adverse events. CI, confidence interval; RR, relative risk.

Sensitivity analysis

When all the outcomes were assessed using a fixed effects model, there was no change in the statistical significance for first variceal bleed (pooled RR, 0.61; 95% CI, 0.44–0.84; $P = 0.003$), overall mortality (pooled RR, 1.07; 95% CI, 0.84–1.35; $P = 0.58$), bleeding-related deaths (pooled RR, 0.63; 95% CI, 0.33–1.20; $P = 0.16$), or adverse events (pooled RR, 0.20; 95% CI, 0.10–0.39; $P < 0.001$).

Table 4 Meta-analysis of variceal band ligation versus β-blockers (full papers and abstracts)

Outcomes[a]	Groups	Patients (*n*)	RR (95% CI)[b]	NNT (95% CI)	*P*-value
First variceal bleed	Full papers and abstracts (16)	1244	0.56 (0.43–0.74)	11 (8–20)	<0.001
	Full papers (9)	734	0.63 (0.43–0.92)	13 (7–33)	0.003
	Abstracts (7)	510	0.40 (0.25–0.66)	9 (6–25)	<0.001
Overall mortality	Full papers and abstracts (16)	1244	1.01 (0.82–1.23)	–	0.81
	Full papers (9)	734	1.09 (0.86–1.38)	–	0.47
	Abstracts (7)	510	0.80 (0.53–1.19)	–	0.27

CI, confidence interval; NNT, number needed to treat; RR, relative risk.

[a]No evidence of statistical heterogeneity for all outcomes.

[b]Random effects model use.

Discussion and compare

- First variceal bleeding
  - No Sig in more larger varices or advanced LV
  - More reduction 37% vs 27-30% (tighter CI)
- Bleeding-related mortality
  - Still Underpower (type II error)
  - Two terminated due to lower event rates

- Adverse effect
  - Band-induced ulcer bleeding: 25 persons
    - (withdrawl 8 persons) -> 2 mortalies
    - Aggressive protocol : qweek, > 10 bands, until eradication (Better in 2 monthly)
    - Post procedure PPI effect !?
  - Overtube perforation
- Mortality
  - 2 person mortality in VBL
  - None in B-block
  - After DC => 13 persons bleeding, 3 mortality
  - Choose adequate patient population
    - < 5mm : increase bleeding rates

Appraisal (治療類文獻)

Level	與[治療/預防/病因/危害]有關的文獻
1a	用多篇RCT所做成的綜合性分析(SR of RCTs)
1b	單篇RCT(有較窄的信賴區間)
1c	All or none
2a	用多篇世代研究所做成的綜合性分析
2b	單篇cohort及低品質的RCT
2c	Outcome research / ecological studies
3a	SR of case-control studies
3b	Individual case-control studies
4	Case-series(poor quality :cohort / case-control studies)
5	沒有經過完整評讀醫學文獻的專家意見

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies *or* extrapolations from level 1 studies
C	level 4 studies *or* extrapolations from level 2 or 3 studies
D	level 5 evidence *or* troublingly inconsistent or inconclusive studies of any level

AA PICO

Answer	VBL could reduce first bleeding rate and less intolerant	
Author	Dhiraj Tripathia, Catriona Grahamb and Peter C. Hayesa Department of Hepatology	無明顯利益衝突
Patient	Randomization, RCT Level 1A, grade A	representative
Intervention	VBL and b-blocker in prevention of variceal bleeding	
Comparison		
Outcome	沒有客觀雙盲的測量	部分有統計學或臨床上的意義
Time	清楚描述研究取樣、操作不清楚、結果測量的時間點，追蹤時間(不定, 13-35 months)	

Primary outcomes

- 1. First Variceal bleeding

Secondary outcomes

- 1. All-cause mortality
- 2. Bleeding-related mortality
- 3. Adverse events

Not blinded

All trials except one [19] met at least three criteria for trial quality (Table 3). This trial did not report on the generation of the randomization list, concealment of treatment allocation and completion of follow-up [19]. Follow-up was not complete in three reported trials [10,21,22], and all patients were included in the final analysis on an intention-to-treat basis. No blinding was performed for outcome assessment in any of the trials. Four trials met the other four criteria, and were considered to be of the highest quality [7,21–23].

Variceal band ligation (VBL)

- Better outcome in
  - first variceal bleed
    - [0.63; 95% confidence interval (CI), 0.43–0.92]
    - NNT: 13 , reduction 37%
  - Adverse events resulting in treatment withdrawal
    - (0.24; 95% CI,0.12–0.47)
    - NNT: 10 , reduction 76%
- No difference in
  - bleeding-related deaths (RR, 0.71; 95% CI, 0.38–1.32)
    - Banding-related bleeding occurred in six patients (fatal in two)
  - overall mortality (RR, 1.09; 95% CI 0.86–1.38)

	Our PICO	This article
P Patient/Problem	LC with Varices of patient without previous bleeding	Varices of patient without previous bleeding
I Intervention	Panendoscopy ligation	Panendoscopy
C Comparison	Non-selective B blocker	Propranolol or Nadolol
O Outcome	Variceal bleeding rate Compliance	Variceal bleeding rate, overall mortality, bleeding-mortality, adverse effect

Valid

Acknowledgement

Conflicts of interest – none declared.

使用work sheet嚴格評讀

TREATMENT WORKSHEET

使用work sheet嚴格評讀

Are the results of this harm study valid?	
Were there clearly defined groups of patients, similar in all important ways other than exposure to the treatment or other cause?	**Yes, there were.**
Were treatment exposures and clinical outcomes measured the same ways in both groups (e.g., was the assessment of outcomes either objective (e.g., death) or blinded to exposure)?	**Yes, they were.**
Was the follow-up of study patients complete and long enough?	**Yes, it was. (partial)**

使用work sheet嚴格評讀

Are the results of this single preventive or therapeutic trial valid?	
Was the assignment of patients to treatments randomised? -and was the randomisation list concealed?	Yes. But not concealed
Were all patients who entered the trial accounted for at its conclusion? -and were they analysed in the groups to which they were randomised?	Yes.
Were patients and clinicians kept "blind" to which treatment was being received?	No.
Aside from the experimental treatment, were the groups treated equally?	no
Were the groups similar at the start of the trial?	Yes.

使用work sheet嚴格評讀

Can you apply this valid, important evidence about a treatment in caring for your patient?	
Do these results apply to your patient?	Yes, it can.
Is your patient so different from those in the trial that its results can't help you?	No, he's not.
How great would the potential benefit of therapy actually be for your individual patient?	Less bleeding rate and more compliance
Method	NNT: 13
Are your patient's values and preferences satisfied by the regimen and its consequences?	Unclear, because different adverse effect

使用work sheet嚴格評讀

Should these valid, potentially important results of a critical appraisal about a harmful treatment change the treatment of your patient?	
Can the study results be extrapolated to your patient?	Yes, it can.
What are your patient's preferences, concerns and expectations from this treatment?(病人的期望、喜好、關心)	Good outcome. Lower discomfort and Adverse Effects , fewer cost
What alternative treatments are available?	TIPS, liver transplant….

將EBM結果應用到病人身上

醫療現況	病人意願
目前肝硬化病人,建議做胃鏡檢查,但往往發現靜脈瘤後,病人想要積極預防治療	病人覺得能用口服藥來減緩疾病惡化時是蠻能夠接受的治療
生活品質	**社會脈絡**
副作用血壓低, 心跳慢, 虛弱, 慢性腎衰竭惡化, 氣喘發作	副作用多, 病人較難長期間規則服用, 而造成用藥中斷, 胃鏡預防性治療在tolerance差的病人, 有重要的治療地位

總結與討論

- 胃鏡預防性治療(band ligation)雖是較為侵入性的治療，但經分析，在適當評估適合病人(EV, > 5mm)情況下，ligation treatment並沒有增加mortality以及procedure bleeding rate ，當病人無法長期接受藥物的副作用情況下，或是口服藥物治療預期無效時，在告知病人風險下，胃鏡預防性治療(eradication)也可以當作第一線的治療。


Thanks for listening