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Effects of Anticoagulants in Patients With Cirrhosis and Portal Vein Thrombosis: a Systematic Review and Meta-Analysis

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LL and FV contributed to the conception and design of the study. All the authors participated in writing the manuscript, and approved the final draft. LL and DP undertook the literature search and retrieval of publications. LL and AF performed statistical analysis.

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Abstract

Background & Aims: Liver cirrhosis is complicated by bleeding from portal hypertension but also by portal vein thrombosis (PVT). PVT occurs in about 20%–50% of patients with cirrhosis, and is a warning sign for poor outcome. It is a challenge to treat patients with cirrhosis using anticoagulants, because of the perception that the coexistent coagulopathy could promote bleeding. We performed a systematic review and meta-analysis to determine the effects of anticoagulant therapy in patients with cirrhosis and PVT.

Methods: We searched the Pubmed, ISI Web of Science, SCOPUS, Cochrane databases through February 14, 2017 for studies that assessed the effect of anticoagulant therapy vs no treatment in patients with cirrhosis and PVT. We performed a meta-analysis to estimate the effect of anticoagulant treatment vs no therapy on recanalization and progression of PVT in patients with cirrhosis. We also assessed variceal and non-variceal bleeding.

Results: We analyzed data from 8 studies, comprising 353 patients, that assessed the effects of anticoagulant therapy (low-weight heparin or warfarin vs no therapy) in patients with cirrhosis and PVT; these studies reported rates of complete and partial recanalization. A significantly higher proportion of patients treated with anticoagulants underwent PVT recanalization than patients that did not receive anticoagulants (71% vs 42%, respectively; P<.0001). From 6 studies (comprising 217 patients), 53% of patients treated with anticoagulants vs 33% of patients who did not receive anticoagulants had complete PVT recanalization (P=.002). From 6 studies (comprising 225 patients), PVT progressed in 9% of patients treated with anticoagulants vs 33% of patients who did not receive these drugs (P<.0001). Six studies (257 patients) reported rates of any bleeding; there was no difference in the proportions of patients with major or minor bleeding between groups that did vs did not receive anticoagulants (11% for both groups). Four studies (comprising 158 patients) reported rates of spontaneous variceal bleeding, which occurred in a significantly lower proportion of patients who received anticoagulants vs those who did not (P=.04).

Conclusions: Based on a systematic review and meta-analysis, patients with cirrhosis and PVT who receive anticoagulant therapy have increased recanalization and reduced progression of thrombosis, compared to patients who do not receive anticoagulants, with no excess of major and minor bleedings and less incidence of variceal bleeding.

KEY WORDS: outcome, complication, LWMH, vitamin K antagonists

Introduction

Liver cirrhosis (LC) has long been considered a clinical setting associated with a coagulopathy-related bleeding risk but this paradigm has been challenged because, apart from gastrointestinal bleeding, spontaneous bleeding is not frequent in LC as depicted by low rate of intracranial hemorrhage compared to control population[1]. Furthermore, both spontaneous and provoked bleedings are unrelated to platelet count and clotting changes[2].

Conversely, there is a growing body of evidence that LC patients suffer also from thrombosis in the portal and systemic circulation[3]. Portal vein thrombosis (PVT) occurs in approximately 20% of LC patients, particularly in those with advanced cirrhosis, and it is considered a hallmark of poor outcomes. However, treating PVT with anticoagulants could be difficult to implement because the coexistence of a coagulopathy may be a potential barrier. Of note is also the fact that the "coagulopathy" of LC patients is difficult to be accurately assessed with standard laboratory indexes such as Prothrombin time(PT)- International normalized ratio (INR)[4]. Despite this, a few studies analyzed safety and efficacy of anticoagulants in LC patients with PVT[3]. A previous meta-analysis on this field reported that anticoagulants might be safe and effective in reducing PVT but inclusion of both comparative and non-comparative studies limits conclusions[5]. In another recent study in PVT patients with and without cirrhosis, anticoagulants were shown to reduce thrombosis recurrence, but no data regarding the effect in cirrhotic patients were reported[6].

To explore this issue, we performed a meta-analysis where only trials comparing the effect of anticoagulant therapy vs no treatment in cirrhotic patients with PVT were included.

Methods

ELIGIBILITY CRITERIA.

Types of studies: clinical studies that assessed the effect of anticoagulant therapy vs no treatment in cirrhotic patients with PVT were included. No language, publication date, or publication status restrictions were imposed. We conducted all analyses according to the intention-to-treat principle. For trials with a factorial design, we based main results on 2-way analyses, that is, all trial participants receiving anticoagulants were compared with all non-anticoagulated treated ones.

INFORMATION SOURCES.

The studies were identified by searching electronic databases. This search was applied to Pubmed, ISI Web of Science, SCOPUS and Cochrane database. The last search was run on February 14, 2017. Reference lists of all studies included in the present metanalysis were screened for potential additional eligible studies.

SEARCH.

Two investigators (D.P. and L.L.) independently searched in the electronic databases combining the following text terms and MeSH terms: (("portal vein"[MeSH Terms] OR ("portal"[All Fields] AND "vein"[All Fields]) OR "portal vein"[All Fields]) AND ("thrombosis"[MeSH Terms] OR "thrombosis"[All Fields])) AND ("liver cirrhosis"[MeSH Terms] OR ("liver"[All Fields] AND "cirrhosis"[All Fields]) OR "liver cirrhosis"[All Fields] OR "cirrhosis"[All Fields] OR "fibrosis"[MeSH Terms] OR "fibrosis"[All Fields]) AND ("anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields]) AND "humans"[MeSH Terms]Studies. We limited our search to human studies.

STUDY SELECTION.

Two authors (L.L., D.P.) independently reviewed titles and abstracts generated by search. Studies were excluded if the title and/or abstract showed that the papers did not meet the selection criteria of our meta-analysis. For potentially eligible studies or if the relevance of an article could not be excluded with certitude we procured the full text. Disagreements were resolved by discussion between L.L. and D.P.; if no agreement reached, a third author (F.V.) decided.

Studies not including an untreated control group and animal studies were excluded. Case reports, editorials, commentaries, letters, review articles, guidelines were also excluded from the analysis.

We defined the following exclusion criteria: (1) studies where portal vein thrombosis developed in non-cirrhotic patients; (2) studies unrelated to our topic; (3) studies where portal vein thrombosis developed after liver transplantation or other major surgical procedures .

Quality assessment

Data quality was evaluated modifying the questions previously reported by Xingshun[5] (see supplementary data, Table 1)

Main analysis

We evaluated the effect of anticoagulant treatment vs no therapy on recanalization and progression of PVT in patients with cirrhosis. Furthermore, variceal and non-variceal bleedings were assessed. This review was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement issued in 2009[7].

Statistical analysis

We allocated the results of each trial as dichotomous frequency data. We considered a P value <0.05 as significant. Odds Ratios (OR) and 95% confidence intervals (CIs) were calculated. Data were pooled and compared with a random-effect model. Meta-regression was performed by means of a weighted regression after log transformation of each OR value. The presence of publication bias was evaluated by using the Egger's test[8]. Statistical heterogeneity was calculated by the I^2 [9]. The I^2 value estimates the amount of variance across studies due to heterogeneity rather than chance. We considered the following scores: I^2 < 30% for mild heterogeneity, 30–50% for moderate heterogeneity, and >50% for severe heterogeneity. The software Comprehensive Meta Analysis (version 2.2.064, USA, 2011) and R (version 3.1.2, Vienna, 2014) supported the

analysis. Presence of publication bias was explored using funnel plots of effect size against standard error.

Results

Eight studies, including 353 patients, assessed the effect of anticoagulant therapy (LWMH/Warfarin vs no therapy) in patients with cirrhosis and PVT[10-17]; clinical characteristics of the studies are reported in table 1. Anticoagulant treatment consisted of low-molecular weight heparin (LMWH) or vitamin K antagonists and lasted about 6 months; follow-up was about 2 years (see table 1).

Eight studies (n=353) analyzed the rate of PVT recanalization, including complete and partial recanalization; recanalization was 71% and 42% in anticoagulant-treated and untreated patients, respectively. Recanalization of PVT was significantly higher in cirrhotic patients treated with anticoagulants compared with untreated ones (O.R.: 4.8; 95% C.I., 2.7-8.7; p<0.0001) (Figure 2, panel A). No heterogeneity (I^2=3.8, p=0.400) among trials was observed; the publication bias was not statistically significant (Egger's test, p=0.07).

Six studies (n=217) analyzed the rate of complete PVT recanalization, that was 53% and 33% in anticoagulant-treated and untreated patients, respectively. Complete recanalization of PVT was significantly higher in anticoagulant-treated patients compared with untreated ones (O.R.: 3.4; 95% C.I., 1.5-7.4; p=0.002) (Figure 2, panel B). No heterogeneity (I^2=9, p=0.356) among trials was observed; the publication bias was statistically significant (Egger's test, p=0.004).

Six studies (n=225) evaluated PVT progression (Figure 2, panel B). The incidence of PVT progression was 9% and 33% in anticoagulant-treated and untreated patients, respectively. The rate of PVT progression was significantly lower in anticoagulant-treated patients compared with

untreated ones (O.R.: 0.141; 95% C.I., 0.06-0.31; p<0.0001) (Figure 2, panel B). No heterogeneity (I^2=0, p=0.461) and no evidence of publication bias (Egger's test, p=0.791) was observed.

Six studies (n=257 patients) reported the rates of any bleeding. No significant difference was found for major plus minor bleedings (11% in both anticoagulant-treated patients and untreated ones). There was no heterogeneity among trials (I^2=18, p=0.293) and no evidence of publication bias (Egger's test, p=0.795) was observed.

Four studies (n=158 patients) reported the rates of spontaneous variceal bleedings; a significant difference was found for variceal bleedings (2% vs 12% in anticoagulant-treated patients vs untreated ones, respectively). The rate of variceal bleedings was significantly lower in anticoagulant-treated patients compared to untreated ones (O.R.: 0.232; 95% C.I., 0.06-0.94; p=0.04) (Figure 2, panel C). No heterogeneity among trials (I^2=0, p=0.618) and no evidence of publication bias (Egger's test, p=0.533) was observed.

Meta-regression analysis (table 2) showed that duration of anticoagulation did not influence outcomes. LMWH, but not warfarin, was significantly associated with a complete PVT resolution as compared to untreated patients, while both LMWH and warfarin were effective in reducing PVT progression. Compared to controls, no excess of bleeding was observed with both anticoagulants while a significant reduction of variceal bleeding was detected with LMWH. Among anticoagulated patients, no difference was found between warfarin and LMWH after adjustment for study typology. Of note, a significantly higher rate of PVT progression was reported in retrospective studies as compared to prospective ones.

Discussion

The results of this meta-analysis shows that, in LC patients with PVT, anticoagulant drugs such as low-molecular weight heparin or warfarin are useful for treatment of thrombosis and its sequalae and are not associated with enhanced bleeding risk.

Since 1970s it has been suggested that LC may be complicated by PVT but the underlying mechanism as well as the clinical impact of this clotting changes were unclear. While the mechanism of hyper-coagulation is still matter of debate[18], the clinical relevance of this finding became evident when observational studies documented an enhanced risk of thrombosis not only in portal but also in systemic circulation[19]. Due to the negative impact of PVT in terms of vascular complications including increase of portal hypertension and bleeding risk, and higher complications in early post-liver transplantation period[20], prevention of thrombotic risk would be an important goal but so far clinical and laboratory variables to adequately assess the thrombotic risk in LC patients are limited. In particular, INR and platelet count are not reliable markers for predicting complications in LC patients[21]. Thromboelastography (TEG) might be a promising tool for monitoring of hemostatic functions in patients with and without LC[22, 23]; it is frequently used during major surgical procedures such as liver transplantation and cardiovascular surgery[24]. However, despite an improved degree of standardization, it still deserves further investigation as no data regarding its predictive value in LC population are available.

Treatment of cirrhotic patients with PVT is challenging because, compared to other clinical settings, in LC carries per se a gastrointestinal-related bleeding risk, which could minimize the potentially beneficial effect of anticoagulants. The present study shows, however, that whatever is the anticoagulants, a beneficial clinical efficacy was detected. This was evidenced by the positive effects in terms of recanalization as well as progression rate of PVT. While complete and

partial recanalization occurred in >70% of patients, complete recanalization was detectable in approximately 50%; these positive effects were observed after approximately 6 months of treatment. Progression of thrombosis was another variable, which was positively influenced by anticoagulants (lower risk of progression or clot regression); thus, if not treated, >30% of patients could experience progression. Of particular interest was the fact that anticoagulant treatment was safe as no increase in major and minor bleedings was seen in anticoagulant-treated patients. Data regarding safety were independent from liver failure degree and are consistent with a previous report in cirrhosis without PVT where anticoagulant treatment did not increase the bleeding risk[25]. We also analyzed if anticoagulants may unfavorably affect variceal bleeding but, conversely, anticoagulants showed to be protective. This is consistent with a previous report in non-cirrhotic PVT showing that anticoagulants protected against variceal bleeding; the authors suggested that thrombosis reduction could limit blood pressure increase in the portal circulation and eventually prevent variceal rupture[26].

Subgroup analysis showed that LMWH treatment was effective for PVT resolution and progression, and was associated with a significant lower rate of variceal bleeding. Conversely, warfarin had similar safety profile but was effective only on PVT progression; however, this result should be interpreted with caution as most studies on warfarin were retrospective, and no data on anticoagulation quality was available.

The study has implications and limitations. An implication of this report is that in cirrhosis with PVT anticoagulants yield >50% PVT recanalization, lower PVT progression and are safe. However, this meta-analysis is limited by the small sample size, which globally included about 350 cirrhotic patients, lack of information regarding site and extension of thrombi and by the fact that results stem from non-randomized controlled trials. Our data would suggest a different impact of

anticoagulation treatments on PVT outcomes but this finding is limited by study methodology and sample size and, thereby, needs to be confirmed by randomized clinical trials. For this reason, it would be also interesting to know the impact of non-vitamin K antagonist oral anticoagulants in PVT of cirrhotic patients.

In conclusion, the results of this meta-analysis show that anticoagulants are efficacious and safe for treatment of PVT in cirrhotic patients but suggest the need of planning interventional clinical trials with larger sample size to corroborate this apparent clinical usefulness.

Figures legend.

Figure 1. Flow-chart of studies: search and selection

Figure 2.

Panel A: Meta-analysis of studies investigating complete recanalization of portal vein thrombosis according to anticoagulant treatment.

Panel B. Meta-analysis of studies investigating progression of portal vein thrombosis according to anticoagulant treatment.

Panel C. Meta-analysis of studies investigating variceal bleeding according to anticoagulant treatment.

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Table 1. Characteristics of studies included in the meta-analysis

Author/ Year	Study Design	Study Population	Anticoagulated patients / controls (*n*)	Age (*years*)	Follow up	Duration of anticoagulation	Type of Anticoagulation	Indexes of LC severity	Thrombotic outcomes			Bleeding outcomes
					Months	Months			PVT Recanalization	PVT unchanged	PVT Extension	
Francoz (2005) [10]	P CS	Cirrhotic patients listed for transplantation	19 treated	49	36	8.1	LMWH (Nadroparin 5700 UI/day) followed by acenocumarol (INR target 2.5)	MELD: 13.0 (overall) CTP: A=26% B=41% C=33%	8/19	10/19	1/19	1 post-procedural bleeding
			10 untreated			-	-		0/10	4/10	6/10	None reported
Garcovich (2011) [11]	R CS	Cirrhotic patients with non-malignant PVT	15 treated	NR	6	3-6	LMWH	Only CTP A and B	7/15	NR	NR	NR
			15 untreated			-	-		5/15			
Senzolo (2012) [12]	P CS	Cirrhotic patients with non-malignant PVT	35 treated***	55.5	24	6	LMWH (Nadroparin 95 antiXa U/Kg body weight td)	MELD: 12.6 CTP: A=11; B=16; C=8.	12/33 complete 9/33 partial (>50%)	7/33	5/33	1 cerebral, 1 epistaxis, 1 haematuria, 1 variceal
			21 untreated	52.3		-	-	MELD: 13.7 CTP: A=5; B=9; C=7.	1/21	NR	15/21	5 variceal
Cai (2013) [13]	R CS	Patients with hypersplenism caused by cirrhotic portal hypertension	5 treated	52.8	37	3	2 pts: LMWH (Nadroparin 85 IU/Kg every 12h) 3 pts: warfarin	CTP: A=4; B=1; C=0.	4/5 all complete	1/5	0/5	None reported

		underwent to partial splenic embolization (PSE).	6 untreated			-	-	CTP: A=2; B=4; C=0.	NR	NR	2/6	1 variceal, 1 variceal with hematemesis, 1 melena
Chung (2014) [14]	R CS	Cirrhotic patients with non-malignant PVT	14 treated	59.4	4	3.7	Warfarin	CTP: A=6; B=8; C=0.	11/14 (6 complete, 5 partial)	2/14	1/14	None reported
			14 untreated	58.7		-	-	CTP: A=7; B=6; C=1.	5/14 (3 complete and 2 partial)	2/14	3/14	1 variceal, 1 subarachnoid hemorrhage
Risso (2014)[15]	R	Cirrhotic patients with non-malignant PVT liver transplantation	50 treated	NR	NR	NR	NR	NR	35/50	NR	NR	17% all minor bleedings
			20 untreated			-		NR	8/20	NR	NR	NR
Chen (2015) [16]	R CS	Cirrhotic patients with non-malignant PVT	30 treated	44.9	33	7.6	Warfarin	MELD: 9.9 CTP: 7.68	15/22	4/22	3/22	4 hematemesis/melena, 1 epistaxis, 3 gingival
			36 untreated	47.8		-	-	MELD: 8.9 CTP: 7.71	4/16	6/16	6/16	None reported
Wang^ (2016) [17]	P RCT	Cirrhotic patients with PVT who underwent TIPS placement	31 treated	54.5	12	12	Warfarin	MELD: 10.6 CTP: 7.3	31/31	0/31	0/31	3 gastrointestinal (1 variceal)
			33 untreated	55.0		-	-	MELD: 7.6 CTP: 10.9	30/32	1/32	1/32	2 gastrointestinal (1 variceal)

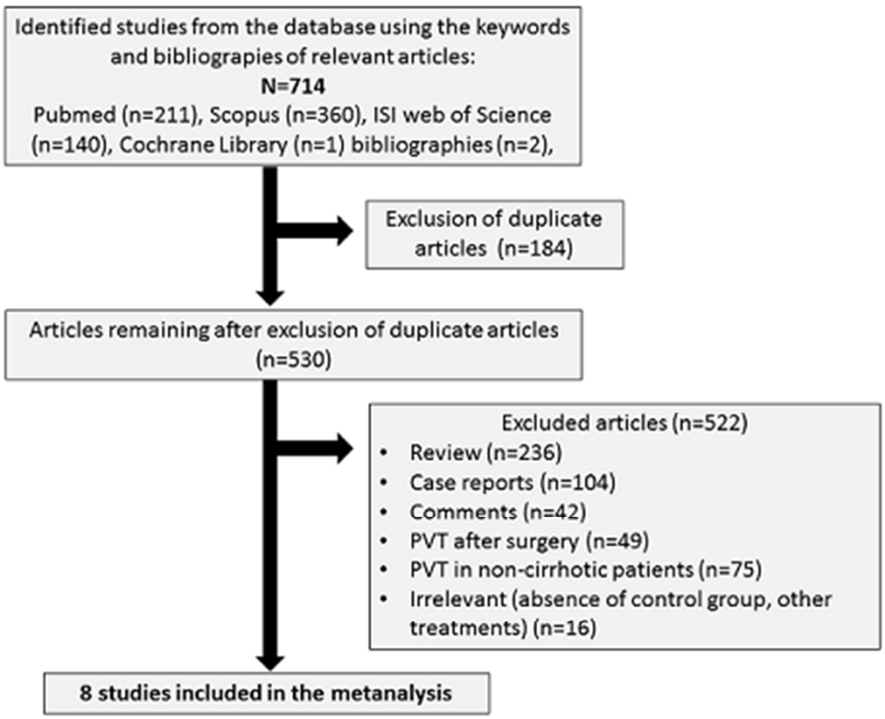
*2 patients with unknown outcome; **1 patient with unknown outcome; ^12-months outcomes; *** two patients were excluded after enrollment. CTP: Child-Turcotte-Pugh, CS: cross-sectional, INR: international normalized ratio, LC: liver cirrhosis, LWMH: low-

molecular weight heparin, MELD: Model for End-Stage Liver Disease, NR: not reported, P: prospective, PVT: portal vein thrombosis, R: retrospective, RCT: randomized control study, UFH: unfractionated heparin.

Table 2. Meta-regression analysis for each outcome

Study-level factors	Complete Recanalization of PVT			Progression of PVT			Variceal Bleeding		
	Pooled OR over subgroup	95% CI	p-value	Pooled OR over subgroup	95% CI	p-value	Pooled OR over subgroup	95% CI	p-value
Duration of anticoagulation (per month)	0.872	0.661-1.152	0.389	1.100	0.826-1.467	0.550	1.264	0.986-1.620	0.206
Type of Anticoagulation									
LMWH (vs. untreated)	8.386	3.287-21.393	**0.011**	0.062	0.040-0.097	**<0.001**	0.103	0.040-0.264	**0.041**
Warfarin (vs. untreated)	2.232	0.742-6.720	0.226	0.338	0.238-0.479	**0.004**	0.713	0.318-1.600	0.499
Warfarin (vs LMWH)	0.266	0.062-1.131	0.147	5.446	3.089-9.960	**0.004**	6.925	2.002-23.952	0.0924
Warfarin (vs LMWH), adjusted by study design	0.057	0.002-1.651	0.194	2.060	0.749-5.664	0.256	4.368	0.158-119.78	0.545
Study Design									
R (vs P)	0.420	0.075-2.349	0.379	5.890	3.642-9.526	**0.002**	6.476	1.284-32.661	0.152

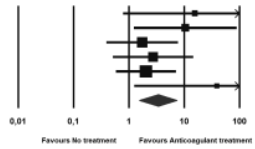
CI: confidence intervals, LWMH: low-molecular weight heparin, OR: odds ratio P: prospective, R: retrospective.



A

Complete Recanalization of PVT

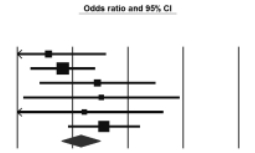
Study name	Odds ratio	Lower limit	Upper limit	p-Value	Anticoagulant treatment	No treatment	Relative weight
Francoz	15,522	0,794	303,254	0,071	8 / 19	0 / 10	6,60
Senzolo	10,435	1,245	87,473	0,031	12 / 35	1 / 21	12,44
Garcovich	1,750	0,400	7,664	0,458	7 / 15	5 / 15	23,90
Chung	2,750	0,524	14,439	0,232	8 / 14	3 / 14	19,53
Wang	2,035	0,595	6,953	0,257	26 / 31	23 / 32	32,50
Cai	39,000	1,277	1190,838	0,036	4 / 5	0 / 6	5,04
	3,385	1,553	7,378	0,002	63 / 119	32 / 98	



B

Progression of PVT

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Anticoagulant treatment	No treatment	Relative weight
Francoz	0,037	0,003	0,399	0,007	1 / 19	6 / 10	11,40
Senzolo	0,067	0,017	0,254	0,000	5 / 35	15 / 21	35,96
Chung	0,282	0,026	3,113	0,302	1 / 14	3 / 14	11,18
Wang	0,333	0,013	8,498	0,506	0 / 31	1 / 32	6,15
Cai	0,164	0,006	4,358	0,280	0 / 5	2 / 6	5,98
Chen	0,370	0,084	1,631	0,189	4 / 22	6 / 16	29,33
	0,141	0,063	0,315	0,000	11 / 126	33 / 99	



C

Variceal Bleeding

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Anticoagulant treatment	No treatment	Relative weight
Senzolo	0,094	0,010	0,873	0,038	1 / 35	5 / 21	39,28
Chung	0,310	0,012	8,292	0,485	0 / 14	1 / 14	18,06
Wang	1,033	0,062	17,282	0,982	1 / 31	1 / 32	24,57
cai	0,164	0,006	4,358	0,280	0 / 5	2 / 6	18,10
	0,232	0,058	0,939	0,041	2 / 85	9 / 73