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### The Concordance of Recursive Partitioning Analysis (RPA) Class Stratification with Survival of Brain Metastases Patients in Mohammad Hoesin Hospital, Palembang, Indonesia

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#### ABSTRACT

**Background:** Recursive Partitioning Analysis is one of prognostic scores, has been validated to any different setting. **Objective:** To identify the concordance of Recursive Partitioning Analysis stratification in survival with brain metastases patients. **Methods:** Retrospective study was performed on brain metastases patients from January 2017 until Desember 2019 based on medical record. The follow up time started from the first diagnosis of brain metastases to death or last follow up. The Kaplan Meier was used to plot survival curves and the log-rank test was used to analyse differences between groups **Results:** Mean overall survival time was 4,67 months with 1,14 months for median survival for all patients. According to scoring, mostly (80,8%) patients were in group 3. The median survival time was 7 months and 2 months for group 2 and 3. **Conclusion:** It has shown relatively congruity survival in BM patients with stratification of Recursive Partitioning Analysis in our institution.

#### 1. Introduction

Brain metastases (BM) is an important and frequent cause of morbidity and mortality in adult cancer patients with incidence estimates ranging from 100.000 to 300.000 patients per year.<sup>(1)</sup> Although affecting only a small percentage of the population, BM is the most common type of intracranial malignancies and a very distressing event in the natural course of systemic cancer because it carries the worst prognosis of all systemic metastases and represents a major cause of death in patients with disseminated disease. Typically, they are related to cancer stage but can also be the first manifestation of an undiagnosed malignancy. Various studies estimate that approximately 10 to 30% of patients with cancer

eventually develop BM.<sup>(2-4)</sup> The incidence of BM from unselected patients with different kinds of tumors ranges from 8% to 10%.<sup>(5)</sup> Lung, breast cancer and melanoma are the primary malignancies that contribute up to 80% of BM.<sup>(6)</sup>

The prognosis of BM patients is usually poor, with a median survival of 1 month and 4 - 6 months in untreated and treated patients, but can be unpredictable in a substantial number of patients, as a result of patient heterogeneity within the population.<sup>(7)</sup> Many clinical factors influence prognosis of BM including performance status, age, extracranial disease and, primary tumour status, have been identified as prognostically relevant. Other factors, such as the

number, size or location of BM, histology of the primary malignancy and interval between primary tumor diagnosis and presence of extracranial metastasis.<sup>(8)</sup>

The presence of BM implies an adverse shift in the course of the primary systemic disease due to its impact on survival and quality of life and to the development of potentially disabling symptoms. Prognosis of the BM is a decisive factor in therapeutic decision making. The goal of treatment is to maintain an optimal quality of life for as long as possible. While the choice of treatment mainly depends on the abovementioned factors. With a lack of proven predictive factors, the decision whether or not to treat BM is mostly determined by the patient's prognosis, the expected benefits of treatment as well as the side effects, and the patient's preferences. Next to neurosurgical treatment and conventional radiotherapy, radiosurgery has acquired a prominent role. New systemic therapies and the development of prophylactic treatment have also increased the number of treatment options.<sup>(9)</sup>

In order to select the most appropriate treatment regimen for the individual patient, it is mandatory to be able to predict the patient's survival prognosis as precisely as possible. Prognostic scores, a useful tool for BM patients, as an estimation of a patient's prognosis can guide tailored treatment for these patients. It is appropriate to recommend more aggressive approaches in patients with good performance status and limited disease and focus on symptom control and palliative measures when the disease is more advanced, or comorbidity preclude aggressive therapy.<sup>(10)</sup>

In 1997, *The Radiation Therapy Oncology Group* (RTOG) published the *Recursive Partitioning Analysis* (RPA) prognostic index for patients with BM. It was the first scoring system to classify BM patients in survivorship's categories. The RPA classification is recommended for predicting patients' prognosis.<sup>(8)</sup> Treatment should be considered for RPA class 1 and 2 while conservative management is generally recommended for patients assigned to RPA class 3. RPA classification is a simple method compared to the

others, that could be applicable in almost different setting of hospital with lack of facility in BM services. This scoring could be useful in BM management due to target treatment. Knowing prediction of the survival time, the clinician could perform the best treatment based on patient condition.

The primary goal of this study was to see the concordance of RPA stratification in survival with setting our patient with BM and to identify the factors that influenced the survival.

## 2. Methods

This is survival analysis study based on medical records data of BM patients in Mohammad Hoesin Hospital from January 2017 until Desember 2019. This study was approved by ethical committee of Mohammad Hoesin Hospital and Universitas Sriwijaya No. 084/kepkrsmhfkunsri/2019.

The selection criteria were as follows pathological diagnosis of primary tumor type and imaging diagnosis computed tomography (CT) and (or) magnetic resonance imaging (MRI) of BM. The eligible criteria included only newly diagnosed patient with BM whom accurate death or follow up were available. A total of 124 cases of patients admitted to our department between January 2017 and Desember 2019 met the selection criteria. Among the patients, 46 cases were lost during follow-up or incomplete data. For each patient, age, sex, performance score, number and distribution of BM, site and status of primary tumor, metastatic extent were recorded. Follow up data was collected from medical records and telephonic contact whenever necessary.

Diagnosis of single or multiple BM was based on the report of radiological examinations (CT or MRI). Diagnosis of extracranial metastases was based on CT of the chest and upper abdomen, bone scintigraphy or ultrasound of the abdomen within 30 days of diagnosis of BM. Patients were considered having a primary tumor of unknown origin if within 30 days of diagnosis of BM no primary tumor had been determined on routine workup. Primary tumor was considered as controlled if primary tumor was managed with curative

surgery, radiation and chemotherapy and there was no clinical and/or radiological suspicion of local recurrence. Patients were considered without evidence of active systemic disease, based on the medical record, there was no evidence of metastases outside the brain and the primary tumor was absent. A synchronous BM is one that is identified within 30 days of diagnosis of the primary tumor, while a precocious one presents prior to the primary malignancy.

RPA class was determined using the following four items: KPS, age, local primary control and presence of extracranial metastases. The RPA group was calculated for each patient and categorized into three groups. Patients with RPA class I are under 65 years old of age, with KPS greater than 70 and controlled of primary and absent of systemic disease. RPA class II are patients older than 65 years old with KPS greater than 70 and uncontrolled systemic disease. RPA class III patients have KPS under 70.

The follow-up time started from the first diagnosis of BM to death or the last follow-up. Overall survival (OS) was defined as the time from the initial diagnosis of BM to the death of the patient or the last follow-up. Survival was calculated from the date of diagnosis of BM to the date of last follow-up or death. Patients who were alive were classified as censored observations at the time of analysis.

Kaplan–Meier curves were plotted for evaluation of survival and the log-rank test was used for univariate analysis. Descriptive statistics were used to summarize the demographic and clinical profile of the patients included in the study. Frequency and proportion were used for categorical variables, while mean and standard deviation for interval/ratio variables. The level of significance was set at  $p < 0.0$ . Statistical analysis was performed using SPSS 22.0 software package.

### 3. Results

A total of 78 patients with BM were eligible for this study. Of this 38 were men and 40 were women (mean age  $52.14 \pm 11.15$  years, range 32 to 73 years). The majority of patients had lung primaries (59 %) followed by breast cancer. In 4 patients, declared as unknown primary. MRI of the brain was available in most of the patients to evaluate the extent of the intracranial disease. Of the 78 patients, 46.2 % had multiple lesions (more than three). Only 14.1% had single lesion. The most common presenting signs and symptoms were headache and motoric dysfunction. 34.6% patients had extracranial metastasis while lung as the most common sites. The primary lesion was controlled only in 24.5 %. The KPS was 70 or more only in 20.5 % of the patients. 17.9 % of the patients were 65 years in age or more. In accordance with RPA grouping, mostly patients (80.8 %) were in group 3 and no patient was in group 1. The characteristic of the subjects was presented in **table 1**.

The life status of the patients was known at the end of the study, 76 patients were dead and only two patients still alive. The mean interval between diagnosis of primary tumor and BM was  $12.58 \pm 29.78$  months and varied widely with the site of primary tumor,  $2.78 \pm 5.02$  months in lung cancer,  $33.19 \pm 49.72$  months in breast cancer. In the whole series, mean overall survival was 4.67 months and median survival time was 1.14 month. Overall survival of the 78 patients was 42.3 % at 3 months and 20.5 % at 6 months, and 14.1 % 1 year. After one year only 11.5% patients still alive. According to RPA stratification, the median survival time was 7 months for patients in Group 2 and 2 months for patients in Group 3. (figure 1 and 2).

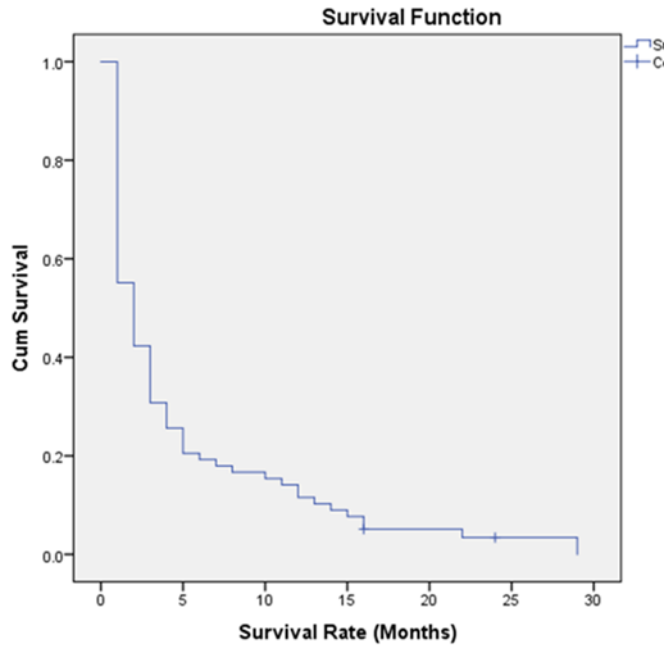
Univariate analysis showed that only RPA group was significant difference to survival. The results of the univariate analysis are detailed in table 2.

Table 1. Patients and Disease Characteristics (n=78)

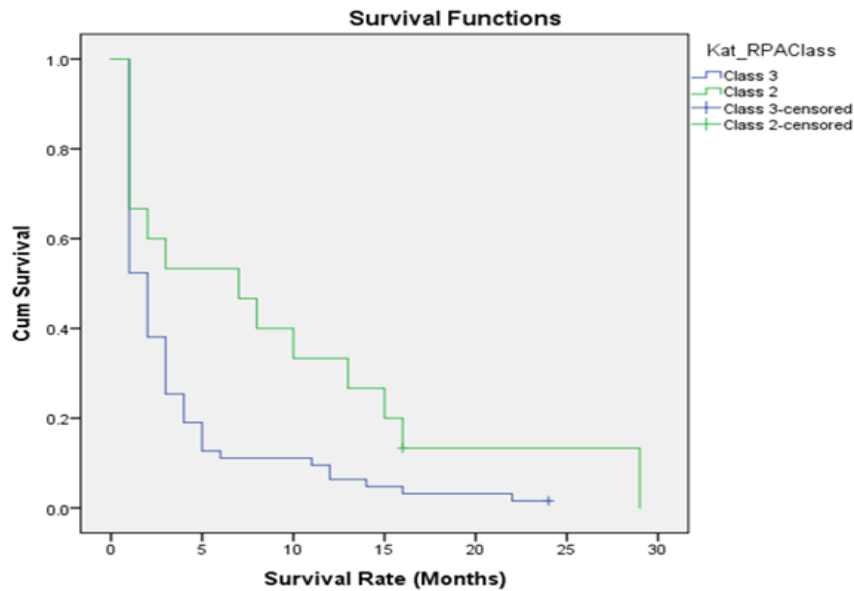
<b>Patients and disease characteristics</b>	<b>n (%)</b>
Sex	
- Male	38(48.7)
- Female	40(51.3)
Age (Mean±SD) years old	52.14±11.15
- < 65	64(82.1)
- ≥ 65	14(17.9)
KPS (Mean±SD)	52.69±13.92
- ≥ 70	16(20.5)
- < 70	62(79.5)
Primary tumor	
- Lung	46(59.0)
- Breast	21(26.9)
- Melanoma	1(1.3)
- Gynaecology cancer	4(5.1)
- Renal	1(1.3)
- Others	1(1.3)
- Unknown	4(5.1)
Controlled Activity primary tumor	
- Yes	19(24.4)
- No	55(70.5)
- Unknown	4(5.1)
Extracranial metastasis	
- Yes	27(34.6)
- No	51(65.4)
Location of extracranial metastases*	
- Lung	11(14.1)
- Spinal cord	2(2.6)
- Bone	9(11.5)
- Liver	9(11.5)
- Lymph node	7(9.0)
- Other	4(5.1)
The timing of brain metastases	
- Synchronous	35(44.9)
- Metachronous	38(48.7)
- Precoex	1(1.3)
- Undefined	4(5.1)
Duration time to BM	
- Less than 1 month	35(44.9)
- 1-6 months	10(12.8)
- >6 months -12 months	11(14.1)
- >12 months	18(23.1)
- Undefined	4(5.1)
The number of brain metastasis	
- Single	10(12.8)
- Oligo (>1-3)	32(41.0)
- Multiple (>3)	36(46.2)
RPA grouping	
- Class 1	0(0,0)
- Class 2	15(19.2)
- Class 3	63(80.8)

Table 2. Univariate analysis on survival

<b>Patients and disease characteristics</b>	<b>n (%)</b>	<b>Median survival (month)</b>	<b>Mean overall survival (month)</b>	<b>Log rank p</b>
Sex				0.643
- Male	38(48.7)	0.76	3.89	
- Female	40(51.3)	0.51	5.15	
Age (Mean±SD) years old				0.151
- < 65	64(82.1)	2.00	5.00	
- ≥ 65	14(17.9)	1.00	2.42	
KPS (Mean±SD)				0.238
- ≥ 70	16(20.5)	2.00	6.06	
- < 70	62(79.5)	2.00	4.14	
Primary tumor				0.241
- Lung	46(59.0)	1.00	3.60	
- Breast	21(26.9)	3.00	6.23	
- Melanoma	1(1.3)	1.00	1.00	
- Gynaecology cancer	4(5.1)	1.00	9.75	
- Renal	1(1.3)	1.00	1.00	
- Others	1(1.3)	1.00	1.00	
- Unknown	4(5.1)	2.00	2.50	
Controlled Activity primary tumor				0.393
- Yes	19(24.4)	3.00	6.52	
- No	55(70.5)	1.00	4.05	
- Unknown	4(5.1)	2.00	2.50	
Extracranial metastasis				0.695
- Yes	27(34.6)	2.00	5.03	
- No	51(65.4)	2.00	4.36	
Location of extracranial metastasis*				
- Lung	11(14.1)	3.00	3.90	0.782
- Spinal cord	2(2.6)	1.00	8.50	0.490
- Bone	9(11.5)	2.00	6.22	0.432
- Liver	9(11.5)	3.00	5.88	0.554
- Lymph node	7(9.0)	2.00	4.85	0.917
- Other	4(5.1)	1.00	1.50	0.127
The timing of brain metastasis				0.389
- Synchronous	35(44.9)	1.00	3.25	
- Metachronous	38(48.7)	2.00	5.86	
- Precoex	1(1.3)	7.00	7.00	
- Undefined	4(5.1)	2.00	2.50	
Duration time to BM				0.439
- Less than 1 month	35(44.9)	1.00	3.25	
- 1-6 months	10(12.8)	2.00	4.60	
- >6 months -12 months	11(14.1)	2.00	5.27	
- >12 months	18(23.1)	2.00	7.00	
- Undefined	4(5.1)	2.00	2.50	
The number of brain metastasis				0.052
- Single	10(12.8)	1.00	1.70	
- Oligo (>1-3)	32(41.0)	3.00	5.40	
- Multiple (>3)	36(46.2)	2.00	4.61	
RPA grouping				0.017
- Class I	0(0,0)	-	-	
- Class II	15(19.2)	7.00	9.13	
- Class III	63(80.8)	2.00	3.57	



**Figure 1. Kaplan-Meier survival curves for all patients.**



**Figure 2. Kaplan-Meier survival curves for patients with BM stratified by RPA.**

#### 4. Discussion

It is worth noting that the incidence of BM seems to be increasing in recent years. The possible reasons that are increased surveillance, improved control of systemic cancer and prolonged survival. In addition, the progress of brain imaging technology has also increased the detection rate of BM. However, macro molecular drugs cannot enter the brain because of the blood-brain barrier, which greatly increases the chance

of BM.<sup>(3)</sup> BM may cause severe and debilitating complaints. Headache, cognitive and behavioural disorders, epileptic seizures and focal deficits usually occur within several days or weeks. These symptoms have a considerable impact on the daily functioning of patients and their family members.

Prognosis of BM is poor and the aim of treatment of BM is in the first place to improve or maintain neurological functioning and in a minority of patients,

the treatment objectives will also include extension of survival time. With maximal management the overall survival rate increases to 10–12 months, although some patients demonstrate a remarkable response to treatment. Determining the best treatment for an individual patient with BM is a complex process that requires a multidisciplinary approach. Not all BM are equal and there are many factors to consider when deciding on an appropriate treatment plan. Previous studies have reported with various results correlated to survival of BM patients in different settings.<sup>(9–16)</sup>

Several previous studies have shown that characteristic primary tumor and the treatment strategy before BM diagnosed was significant to the course of BM.<sup>(11,17)</sup> Lung cancer is the most common primary tumor and usually diagnosed at the same time of the diagnosed BM (synchronous).<sup>(7)</sup> Those findings were likely with our study that found the most common type of primary tumor was lung cancer, which accounts for approximately more than half of the BM, followed by breast cancer. BM was diagnosed as synchronous with lung as the primary tumor in majority patients. Contrast to breast cancer, average patients diagnosed were as metachronous BM and 61% systemic disease were controlled in this group. This condition correlated with longer survival of the patients compared to synchronous BM. These results were similar that type of primary tumor was associated with occurrence of BM.<sup>(8,12,13,16)</sup>

In majority, it was considered patient had more than single symptoms of neurological dysfunction at the time of BM diagnosis and the primary tumor were diagnosed at the same time. These findings were similar to others studies. Most studies found that diagnosed of BM due to neurological symptoms. Imaging diagnostic was seldom to performed without indication. Only a few studies performed imaging diagnostic as a routine assessment. Our study showed that neurological symptoms was found in the whole series and being a marker for established of BM.

Treatment of BM is now individualized, with more emphasis placed on balancing treatment effectiveness against neurotoxicity. In patients with good prognosis,

the goal of therapy has shifted from short-term palliation to long-term survival and quality of life (QOL). WBRT is regarded as the standard therapy in an attempt to delay the progression of the intracranial disease for those having shorter life expectancy. More aggressive approaches such as surgery or stereotactic radio surgery (SRS) are indicated in a subset of patients only in an attempt to eradicate the intracranial disease constitutes the treatment strategy for those having longer life expectancy.<sup>(18)</sup> In the other hand, corticosteroid is still needed to improve neurological symptoms in most cases.<sup>(19)</sup> Hence, the ability to foresee the survival probabilities in patients with BM might enable the allocation of these patients to conservative as opposed to aggressive treatment strategies. Survival was dependent on presenting symptoms of BM and treatment received. Accurate prognostic information is useful to optimise treatment for patients who may gain months to years of survival following intracranial progression and to avoid overtreatment of patients who will derive little benefit.<sup>(12,20,21)</sup>

Traditionally, the most commonly used prognostic index is the recursive partitioning analysis (RPA). RPA grouping has been described by the RTOG in order to provide a stratification tool for patients with BM with regard to their allocation to distinct treatment strategies. Through the use of RPA grouping, novel treatment strategies might be investigated in groups of patients with BM. This classification is based on 4 parameters: age, Karnofsky Performance Status (KPS), presence or absence of extracranial metastases and the status of the primary tumor using this approach, median survival ranged from 7.1 months in patients with the best prognostic score (RPA class 1), 4.2 months in RPA class 2 to 2.3 months in those with the worst (RPA class 3).<sup>(8)</sup> Evaluation of these factors is important in identifying patients who will likely benefit most from aggressive treatment, as well as avoiding overtreatment of patients who are unlikely to benefit. In patients with a favourable prognosis (RPA class 1, some class 2), increasing overall and functional neurological survival are reasonable goals and thus focal therapies form a major component of treatment

and outcome assessment includes neurocognition and quality of life. In patients with an unfavourable prognosis management focuses on symptom palliation as needed. (4)

In this retrospective analysis, we aimed to evaluate the concordance of RPA stratification with setting our BM patients. Contrast to previous study, there was no patients in grup RPA 1. In addition, the overall survival time of our patients was generally poor with median survival time not exceeding 3 months. Comparing with stratification of RPA of the RTOG, our study analysis revealed similar median survival rates for grup 3. In grup 2, our study found the higher median survival rate compare RPA (7 months vs 4,2 months). However, the RPA allocates most of the patients into class 2 while in our study more than half patients in grup 3.(8)

Comparable survival times have been shown by previous others studies with various results. Study by Lorenzoni et al found that 55% patient in RPA class 1. Only 10% in class 3 with median survival 27.6 month in class 1, 2.8 months class 3 and 10.7 months for class 2. All patients in this study received SRS as a part of the treatment for BM. (12) Study by Saito et al found the median survival in class 1 was 6.2 months, 4.2 months for class 2 and 3 months for class 3. This study had similar population such our study while the majority of subjects in RPA class 3 (55,9%). In Indoensia population, Gondhowiarjo et al found that 50% of patients were categorized into RPA class 2, 38.7% of patients were categorized into RPA class 3 and the rest 11,2% were categorized into RPA class 1 with median survivals were 16.3 months, 11.2 months and 4.7 months for RPA class 1, RPA class 2 and RPA class 3, respectively.(13) Both of the studies put WBRT as a standar therapy in whole subject with or without surgery or SRS.(13,14)

This differences in survival between our patients and the other studies in same RPA categories could be explained that expected variation in applying this classification. Unlike the previous studies, there was no patients in RPA class 1 and the majority patients were in RPA class 3. However, the functional status of patients reported in these series was generally poor

compared with those reported before, probably because of limited diagnostic capabilities leading to more advanced symptoms before referral for treatment and awareness of the patients was different. Unlike the most studies formerly, all patients were participated in this study without specific category in term primary tumor type, characteristic of intracranial lesion or treatment strategy such other studies. Treatment strategy that offered in our institution was limited. Another major limitation was definition of class 3. Class 3 contained all patients with KPS <70. Assesment of KPS allow some subjectivity in their application. In addition, lower KPS value might result from different etiologies, including BM, systemic disease, other medical conditions. Patients with BM usually receive multimodality treatment including surgery, radiation therapy, and systemic therapy, but in our sample, most patients were in paliatif treatment due to poor performance. In this study. There was no aggressive treatment in BM according to lack of KPS status and aggressive approach like SRS was unavailable in our institution. Surgery its self was done just for diagnostic in minority cases. In group patients with RPA 3 majority got paliatif treatment. Moreover, we did not analyse data regarding administered therapies before diagnosis of BM and we did not have information regarding specific complications of the disease, which led to death. This would be of interest because extracranial disease represents a major limitation on survival.

The RPA has been tested for various treatment scenarios and they have been found to be useful in providing prognostic value in various different settings. Despite the limitations of this study, it is still reasonable to conclude that the RPA was found to offer a better prognostic indicator and deemed to be a valid prognostic scoring system for patients with BM in developing country such Indonesian while majority patient characteristics, major tumour histology, treatment options available and patient's preferences are different. Furthermore, the RPA which includes the age, performance status, extracranial metastases and control of primary tumour, is a simple tool to use in



daily clinical practice. The information required for RPA scoring does need excessive or costly procedures to obtain and no information regarding the number of BM lesions is necessary, because this information may not be readily available. Thus RPA may be a good option to select and use in developing countries that may be resource constrained.

## 5. Conclusion

Even RPA has several limitations, but in institution with minimal resources and health facility, it is very useful tool for clinician in order to choose the treatment strategy of BM. However, as a guide and as a starting point, the RPA prognostic stratification system can be used to provide a rough prediction of prognosis. This study has shown a relatively congruity survival in BM patients with stratification of RPA in our institution.

## 6. Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest related to this study.

## 7. Funding statement

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## 8. Author contribution

Conception and design: YD, SM, A. Collection and assembly of data: all authors. Data analysis and interpretation: YD, SM. Manuscript writing: YD, SM, A. Final approval of manuscript: all authors

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