

# Additional value of microvascular flow imaging in the assessment of cystic and solid renal lesions

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Received: July 24, 2022 • Accepted: December 7, 2022

Published online: February 8, 2023

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## ABSTRACT

*Background:* Contrast enhanced ultrasound (CEUS) is increasingly used in the evaluation of renal lesions, however, its availability remains limited. Thus, sensitive noncontrast ultrasound evaluation of renal lesion vascularity is an unmet need. *Methods:* In this single-center, retrospective study we assessed microvascular flow imaging (MV-flow) compared to CEUS in the evaluation of complex renal cysts and solid lesions. Out of 92 patients 28 were evaluated with both CEUS and MV-flow. Color Doppler, CEUS, and MV-flow was performed in 13 cases, whilst MV-flow, CEUS, and contrast-enhanced MV-flow (CE-MV-flow) was done in 16 cases. The CEUS diagnosis was considered gold standard. *Results:* MV-flow showed a substantial agreement with the CEUS diagnosis (weighted Kappa = 0.806), excluding equivocal lesions (Bosniak 2F). MV-flow substantially outperformed color Doppler (weighted Kappa = 0.77 vs. 0.133). The agreement of CE-MV-flow and MV-flow was comparable (weighted Kappa = 0.79 vs. 0.69). *Conclusion:* MV-flow significantly improves evaluation of renal lesion vascularity compared to conventional techniques. However, the sensitivity is limited for equivocal lesions (e.g. Bosniak 2F cysts). Thus, MV-flow should be used as an ancillary technique, not as a substitute to CEUS. Current MV-flow presets are ill-suited for postcontrast imaging, therefore specific presets optimized for this purpose are needed to establish its potential.

## KEYWORDS

CEUS, contrast-enhanced ultrasound, microvascular flow imaging, MV-flow, Bosniak classification, renal complex cystic masses

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## INTRODUCTION

In the last two decades contrast enhanced ultrasound (CEUS) has been increasingly utilized in the evaluation of both solid and cystic renal mass lesions [1–5]. This is particularly due to its unique advantage over cross-sectional imaging, coupling high spatial resolution with a dynamic, continuous evaluation of contrast enhancement, rather than demonstrating enhancement in distinct phases. The lack of ionizing radiation, rarity of adverse contrast media reactions, no long-term concerns of contrast agent deposition (in case of MRI) are further advantages of this technique over cross-sectional imaging. It has been shown that renal CEUS has comparable performance to CT in the assessment of renal complex cysts and mass lesions [6–10]. The superior temporal and (in case of optimal patient body habitus) spatial resolution gives this technique distinct advantage in evaluating subtle differences in contrast enhancement, coupled with the fact that the most widely used CEUS contrast agent (SonoVue/Lumason) remains intravascular. It has been demonstrated that CEUS has distinct advantage over CT in the depiction of internal septation, intracystic solid component, and their vascularization, thereby being capable of upgrading or reclassifying renal cystic lesions on the Bosniak scale [11–14]. It has also been shown recently that CEUS is an excellent choice for follow-up of equivocal (Bosniak 2F) lesions [15]. Comparison of CEUS and MRI also demonstrated similar results with CEUS having higher diagnostic sensitivity and accuracy, but lower specificity than MRI in the characterization of renal cystic masses [16]. The high sensitivity of CEUS together with a relatively lower specificity was corroborated by further studies, thus proposing it primarily as a rule-out test for renal malignancies [17]. The noninferiority of CEUS compared to CT/MRI was also supported by a recent meta-analysis [18], and a comparison to subsequent histopathology [19]. Another recent meta-analysis of the performance of CEUS in renal lesion characterization found remarkable heterogeneity of the specificity of CEUS between studies. This suggests the need for development of standardized Bosniak CEUS classification systems [20].

Nonetheless, noncontrast ultrasound remains one of the main methods used in the initial detection of renal lesions, and is still far more accessible outside major academic centers than CEUS. Therefore, evaluation of the vascularity of such lesions without administration of ultrasonic contrast material is an unmet need. Unfortunately, color and power Doppler ultrasound imaging lacks the sensitivity for the small caliber vessel flow that would allow the reliable assessment of e.g. vascularity within the septae of complex cysts. As a result the diagnostic performance of conventional ultrasound is substantially lower than that of CEUS in the characterization of complex renal cystic masses [21]. However, recent developments in ultrasound technology such as microvascular flow imaging/superb microvascular imaging (MV-flow) have significantly improved the sensitivity of noncontrast vascular imaging, primarily by more selective suppression of clutter and motion-derived artifacts. This in turn allows assessment of smaller caliber vessels, thus opening up ways to assess microvasculature within renal lesions without contrast agents. Several studies have already demonstrated increased sensitivity of the technique for slow flow and flow within smaller vessels of a variety of tumors [22–26].

It has been shown relatively early that conventional color Doppler ultrasound (CDUS) of renal lesions can be improved by addition of ultrasonic contrast media, however with the advent of low mechanical index (MI) CEUS presets and more stable ultrasonic contrast media this approach was quickly abandoned [27]. More recent studies have however also shown that MV-flow can be used as an adjunctory tool after the administration of ultrasound contrast



media (CE-MV-flow). It has to be emphasized that CEUS does not depict flow, but only resonating contrast agent microbubbles (whether idle, adherent, or moving within vessels). Thus, CE-MV-flow theoretically has the potential to add further value by combining the increased sensitivity of MV-flow for small vessel flow, and the increased contrast due to the presence of microbubbles.

In the current retrospective study we have aimed to assess the performance noncontrast MV-flow imaging in comparison to CEUS, and also to evaluate the potential of CE-MV-flow. We have also demonstrated some of the technical challenges and specific artifacts occurring during pre/postcontrast evaluation of renal masses and cystic lesions.

## MATERIALS AND METHODS

### Study design

This was a retrospective study of the period between September 2019 and March 2020. The study was conducted in accordance with the Declaration of Helsinki, and approved by the Clinical Centre of the University of Pécs (KK/551 1/2020) as well as the Regional Committee on Research Ethics of the University of Pécs (8906-PTE2021, date of approval: 17.09.2021). Requirement for individual informed consent was waived due to the retrospective nature of the study. All patients have signed the general institutional informed consent form for the CEUS exam. In total 92 patients presented for evaluation of newly discovered complex cystic renal lesions and masses during this period. In all cases CEUS was preceded by noncontrast evaluation, and in 10 cases no CEUS exam was conducted (follow up of confirmed lesions, or CEUS not warranted in light of the “second look” noncontrast exam). In the study the reported Bosniak category indicated on the formal CEUS report was considered to be the gold standard. MV-flow, CE-MV-flow, and color Doppler categorization was conducted retrospectively. MV-flow assessment prior to the CEUS exam was conducted and sufficiently documented for retrospective assessment (with multiple single image snapshots and cine recordings) in 28 cases out of the 92. MV-flow was used with either split screen/overlay display depending on the operator’s preference. Color Doppler and MV-flow, as well as CEUS was done in 13 patients. Both precontrast and CE-MV-flow assessment was done in 16 cases. The categorization based on MV-flow compared to CEUS has been summarized in [Supplementary table 1](#). By the time of the retrospective evaluation 7 patients had undergone surgical treatment in our hospital system.

### CEUS and MV-flow exam technique

All CEUS exams were conducted under the direct supervision of two experienced users (ÁJ, and PIF), each with more than 10 years of experience with the modality. All exams were done on the same ultrasound scanner (Samsung RS85, Samsung, Seoul, South Korea), with the same curvilinear array transducer (model: CA1-7A). CEUS was preceded by thorough B-mode evaluation, color Doppler and/or MV-flow assessment. The contrast agent was in all cases SonoVue® (Bracco, Milan, Italy), administered i.v. into the upper extremity veins as a bolus of 1.2–2 ml, followed by a 10–20 ml saline chaser. The timer was started in all cases at the completion of the contrast agent injection. All studies were documented electronically, and cine loops were recorded in the early arterial phase (from the arrival of the first microbubbles to the end of



the first minute after injection). The later phases were followed with repeated interval scanning (to reduce premature microbubble destruction) and acquisition of single image snapshots. CEUS exams were performed with a low mechanical index (0.069–0.07), and with a split screen display technique. During the assessment factors like presence and complexity of septae, internal echogenic content, wall thickening, and calcifications, as well as solid internal nodules all contributed to the final CEUS Bosniak grade as reported previously [6]. CE-MV-flow was conducted in several cases, but only after completion of the formal CEUS exam in the late venous phase due to its high MI.

### Data analysis and statistics

All stored images, cine recordings, and the reports were retrospectively reviewed by two of the authors (ÁJ and BB) during the study in a non-blinded fashion, final assessment was based on consensus. In patients with multiple lesions only the one with the highest Bosniak grade based on CEUS was included in the study. Statistical analysis was performed using the GraphPad QuickCalc calculator and the GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA) software. Comparisons between CEUS, MV-flow, and CDUS were conducted using Fleiss' kappa statistic, relative sensitivity by the Fisher's exact test. Quantitative results (lesion size and depth) were compared using unpaired *t*-test.

## RESULTS

### Summary of the investigated patient population, B-mode structure, and CEUS diagnosis of the lesions investigated

Of the patients involved 59.7% (55/92) were male, and 40.2% (37/92) were female. The median age was 67 years. The median size of the investigated renal lesions was 25 mm (range: 3–147 mm). Lesions were categorized based on the most defining B-mode imaging features, showing that thin septations (21 cases), solid masses (18 cases), and intracystic solid content were the most common findings on noncontrast ultrasound imaging (Supplementary Fig. 1A). The reported formal Bosniak category of the lesions showed that the majority fell into the B2 (22 cases), B2F (17 cases) group, followed by enhancing masses and the B1 cyst (12 cases each) category (Supplementary Fig. 1B).

### Comparison of MV-flow to CEUS in the assessment of the renal lesion vascularity

In 28 cases were MV-flow and CEUS simultaneously performed and documented sufficiently to allow retrospective categorization based on the previously defined criteria. In these cases Fleiss' kappa statistic was used to assess agreement between CEUS and MV-flow. Overall weighted kappa index was found to be 0.806 indicating substantial consistency between the methods by the Landis-Koch scale (Table 1). In 6 cases were results discordant, and in all of these CEUS upgraded the category of the lesion (4 lesions to B2F, 2 lesions to B3).

The mean size of the lesions with concordant and discordant diagnoses was almost identical ( $P = 0.94$ , unpaired *t*-test), whilst the mean depth of the discordant lesions tended to be greater ( $P = 0.08$ , unpaired *t*-test), however not significantly (Supplementary Fig. 2A–B).



Table 1. Discordant results highlighted by bold font (SE = standard error, CI = confidence interval)

Agreement between MV-flow and CEUS by categories and overall Kappa-index

MV-flow	CEUS					
	B1	B2	B2F	B3	B4	Mass
B1	3					
B2		8	<b>4</b>	<b>2</b>		
B2F			5			
B3				2		
B4					2	
Mass						2

Overall Kappa = 0.721 (SE = 0.101, 95% CI = 0.523–0.919) Weighted Kappa = 0.806.

Lesions were also being stratified into two categories, benign (B1–B2F), and malignant (B3–mass). Fleiss' kappa statistic again showed good agreement (Kappa = 0.811) between CEUS and MV-flow ([Supplementary table 2](#)).

Next, we have evaluated relative sensitivity of MV-flow with the same benign vs. malignant categorization, using the formal CEUS diagnosis considered as a gold standard, with Fisher's exact test, which demonstrated a good sensitivity and specificity summarized in [Table 2](#).

[Supplementary Fig. 3](#) illustrates a Bosniak 2F cyst where results were concordant, and MV-flow demonstrated the vascularity of the hairline septae.

[Supplementary Fig. 4](#) shows a Bosniak 2F cysts where only speckled artifacts could be seen behind calcific foci using MV-flow, similarly to CDUS.

[Figures 1 and 2](#) demonstrate Bosniak 3 cysts with concordant and discordant results, also showing that with MV-flow the discrete vascularity shown as "string of beads" microbubble flow by CEUS is particularly difficult to detect.

## Histopathological results

Only 7 lesions that were evaluated with both CEUS and MV-flow went under resection by the time of the study. Among the resected lesions one was found to be a benign tumor (oncocytoma) during histopathological assessment, whilst the rest proved to be different subtypes of renal cell carcinoma ([Supplementary table 3](#)). It has to be emphasized that many patients were referred by external centers, thus the actual number of operated lesions is likely to be higher (the authors only had authorized data collection request to the local electronic health records).

Table 2. Relative sensitivity, specificity and predictive value of MV-flow compared to CEUS

	Value	95% CI
Sensitivity	0.75	0.40–0.95
Specificity	1.0	0.83–1.0
Positive predictive value	1.0	0.60–1.0
Negative predictive value	0.90	0.72–0.98

$P < 0.0001$  (Fisher's exact test).



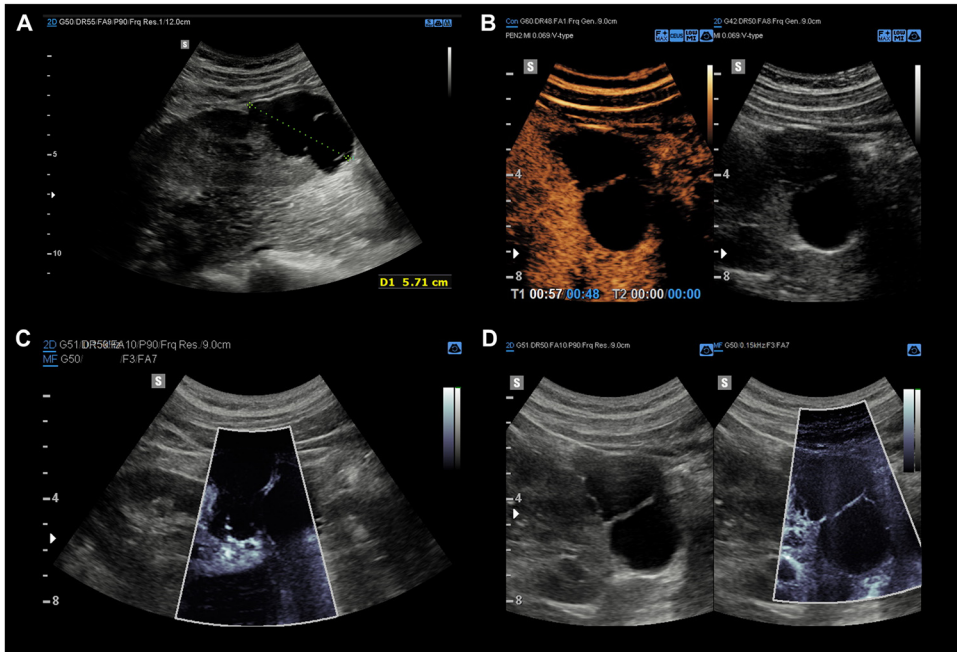


Fig. 1. Bosniak 3 lesion with concordant CEUS and MV-flow findings. A) On B-mode moderately thickened internal septae are visible, which C) show significant contrast agent influx on CEUS. Both C) precontrast, and D) postcontrast MV-flow also displays septal vascularity. Pathologically proven multilocular cystic RCC

### Assessment of the performance of MV-flow and color-Doppler imaging compared to CEUS

Within the study period 13 lesions have been documented to undergo both CDUS and MV-flow imaging at the time of the CEUS exam. Among these lesions MV-flow showed a superior (substantial) agreement with the CEUS exam in contrast to CDUS (slight agreement) demonstrating a better correlation with the CEUS diagnosis, and substantially lower amount of discordant diagnoses (Table 3).

### Evaluation of MV-flow pre- and postcontrast compared to CEUS

CE-MV-flow of renal lesions was conducted in 16 patients, and never before the completion of the formal CEUS exam, due to the MI resultant microbubble decay. For MV-flow and CE-MV-flow the number of discordant diagnoses was 5 and 4 in this subgroup, respectively (Table 4). Both methods demonstrated substantial agreement with the formal CEUS categorization, with CE-MV-flow demonstrating slightly higher agreement (weighted Kappa 0.79 vs. 0.69 with MV-flow).

It has to be noted that while CE-MV-flow generally better demonstrated septal flow in some cases (Fig. 1), there were examples where the flow visualized with noncontrast imaging was



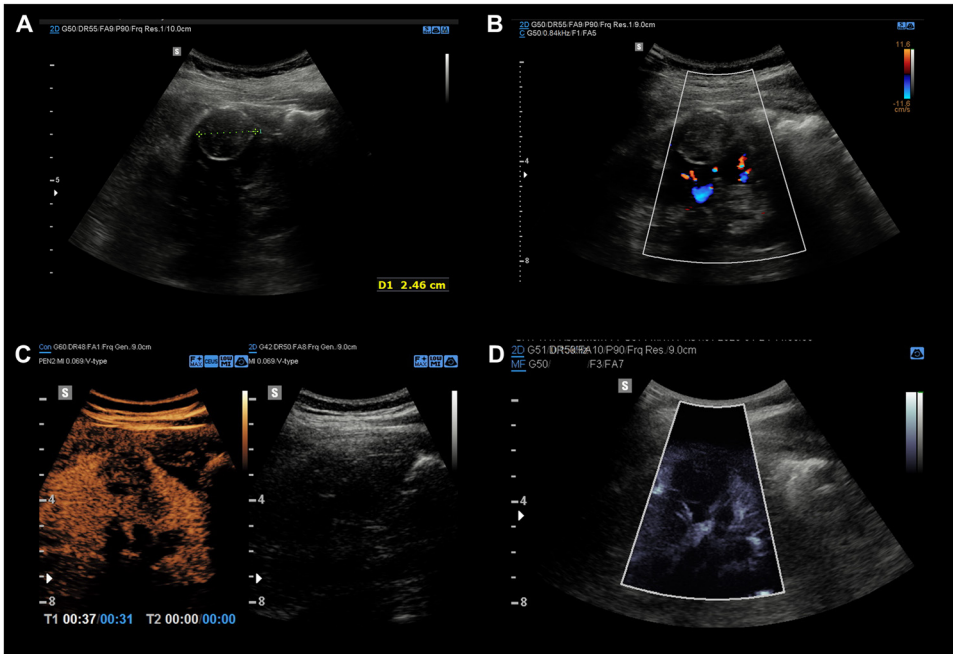


Fig. 2. Bosniak 3 lesion with discordant CEUS and MV-flow findings. A) B-mode displays echogenic internal content, septal and wall thickening, while B) CDUS shows no internal vascularity. C) CEUS shows inhomogeneous internal enhancement. D) MV-flow displays no internal vascularity. Pathologically proven cystic pRCC

Table 3. Agreement between CEUS and color Doppler and MV-flow respectively

	Color Doppler	MV-flow
Kappa	0.158	0.678
SE of Kappa	0.107	0.157
95% CI	-0.05-0.36	0.37-0.98
Weighted Kappa	0.133	0.77
Landis-Koch agreement scale	Slight agreement	Substantial agreement
Discordant diagnoses/total	9/13	3/13

SE = standard error, CI = confidence interval.

degraded by pixelation, increased noise, and ring-down like posterior image degradation behind larger vessels containing large amount of microbubbles (Supplementary Figs 5 and 6).

## DISCUSSION

In this study we have shown that MV-flow outperforms conventional color Doppler imaging in the characterization of renal lesions when compared to CEUS. In the small percentage of cases where both MV-flow and CE-MV-flow was performed, the latter showed a slightly better



Table 4. Agreement between MV-flow and CE-MV-flow and CEUS respectively

	CE-MV-flow	MV-flow
Kappa	0.67	0.58
SE of Kappa	0.14	0.14
95% CI	0.39–0.94	0.29–0.87
Weighted Kappa	0.79	0.69
Landis-Koch agreement scale	Substantial agreement	Substantial agreement
Discordant diagnoses/total	4/16	5/16

SE = standard error, CI = confidence interval.

agreement in comparison to CEUS. The performance of MV-flow was not found to be influenced by lesion size or distance from the skin surface.

In our study the performance of MV-flow was particularly lower for lesions where vascularity is subtle/equivocal (notably B2F cysts). CEUS with its superior ability to depict trickle-like flow of occasional microbubbles within the internal septations of such lesions surpasses MV-flow, which – similarly to other noncontrast techniques – relies on flow-derived signal. It has been recently shown that CEUS has a comparable performance in the assessment of these particularly challenging, equivocal (B2F and B3) lesions to contrast enhanced CT [28]. Furthermore, a recent study using a microvascular imaging technique by a different manufacturer has also found a relatively lower sensitivity of MV-flow when compared to CEUS [29]. In contrast, a very recent study published after the completion of our investigation showed that microvascular imaging has a comparable performance to CEUS in demonstrating vascularity within solid renal lesions [30]. A case-control study of Bosniak 3 lesions has recently found that CEUS might lead to overclassification compared to cross-sectional imaging [31]. This also highlights the necessity to develop standardized Bosniak CEUS classification systems.

Our results demonstrate a marked advantage of MV-flow over color Doppler imaging, both in terms of spatial resolution, and ability to detect flow in small intralésional structures such as septae. This is in good agreement with several very recent studies where microvascular imaging has also been shown to have significant advantage in depicting septal flow within cystic renal lesions, and also within solid lesions of the kidney [29, 32, 33]. Altogether we can conclude that in noncontrast US MV-flow should be preferred over color Doppler for investigating renal lesions, whenever available.

The potential of CE-MV-flow has been previously demonstrated in various applications [34, 35]. Our data demonstrate a modest advantage over MV-flow with several technical caveats. We have found that noise (particularly in the near-field) is facilitated post-contrast, and that pixelation of flow signal can occur in the contrast-filled vessels, hampering spatial resolution. Further ring-down-like artifacts encountered behind larger caliber vessels also contribute to increased noise and thus limited ability to assess tissues lying underneath. Thus, we conclude that standard MV-flow presets are ill-suited to investigate postcontrast flow. It has to be also added again that due to the higher MI of MV-flow (and due to only being performed occasionally as an ancillary technique), it was in all cases used only after completion of the standard CEUS investigation, thus our conclusions only apply to late venous phase signal characteristics.

Our study has several limitations. Most importantly this being a retrospective study the numerous lesions could not be included as either image documentation did not allow confident





evaluation of lesion characteristics on MV-flow/CE-MV-flow, or the technique was not employed. This also raises the likelihood of selection bias, where “promising” lesions (larger, more complex, and/or better visualized) were more likely to be evaluated by this technique. Furthermore, retrospective evaluation was done using a non-blinded, expert consensus approach by the authors. The readers were aware of the results of available prior imaging examinations (e.g. noncontrast ultrasound, CT, or MRI). Only a small subset of lesions were resected, which did not allow direct comparisons with histopathological results. From a technical standpoint MV-flow setups were designed with noncontrast imaging in mind, thus the strong signal given by the contrast agent can actually deteriorate signal to noise ratio, and ring-down effects can occur behind larger vessels. To better evaluate the value of CE-MV-flow dedicated low MI presets tailored to postcontrast imaging are warranted.

Altogether we conclude that using MV-flow as an ancillary technique has a superior diagnostic yield than color Doppler, and has a substantially higher chance to detect internal vascularity of renal lesions. However its sensitivity is significantly lower for borderline (B2F in particular) lesions, thus it should not be used as a standalone tool at this point. Nonetheless, further investigations with prospective study design are clearly warranted. CE-MV-flow is a promising technique, but further optimization of this approach is warranted. In the immediate future use of MV-flow should be encouraged in noncontrast ultrasound imaging of renal lesions.

## CONCLUSIONS

Our findings indicate that MV-flow is a valuable ancillary tool in the noncontrast ultrasound evaluation of renal cystic and solid masses, and has a much better positive predictive value when compared to Doppler Ultrasound. While CE-MV-flow is slightly better than MV-flow in this respect, it is more prone to be influenced by noise, and is less sensitive to very subtle flow (in particular the trickle of almost individual contrast agent microbubbles in B2F lesions). Thus, considering the higher mechanical index of the technique, and the appearance of artifacts post-contrast (the observed pixelation/blooming phenomenon) development of MV-flow presets optimized for postcontrast use is warranted.

*Conflicts of interest:* The authors declare no conflict of interest.

## ACKNOWLEDGMENTS

The authors express their gratitude towards Sonarmed Ltd. for providing technical support. B.B. was supported by the János Bolyai Research Scholarship of The Hungarian Academy of Sciences and the ÚNKP-21-5-PTE-1337 New National Excellence Program of the Ministry for Innovation and Technology.

## SUPPLEMENTARY MATERIALS

Supplementary data to this article can be found online at <https://doi.org/10.1556/2060.2022.00133>.



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