"Role of Ultrasonography and Magnetic Resonance Imaging in Characterisation of Ovarian Masses – Histopathological Correlation and Etiological Stratification"

VIPIN KUMAR BAKSHI¹

DEPARTMENT OF RADIO-DIAGNOSIS, DR. S. S. TANTIA M.C.H & R.C., SRI GANGANAGAR, RAJASTHAN (INDIA)

*Corresponding author – DR. VIPIN KUMAR BAKSHI

Abstract:

Introduction: Adnexal masses pose a diagnostic dilemma to the gynaecologist as well as radiologist because of their varied spectrum. The most important thing that needs to be determined is that whether the lesion is benign or malignant, so that the patient gets the appropriate treatment based on the pathology. Hence, the aim of the present study was to determine the accuracy of MRI in diagnosing benign and malignant adnexal lesions and its correlation with histopathological findings.

Materials and Methods: Prospective cross-sectional study was conducted in the Department of Radio-Diagnosis and Imaging, Jan Sewa Hospital, Sri Ganganagar on 30 patients who were clinically suspected to have pelvic lump/mass or detected with an ovarian mass incidentally on USG.

Results: The sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, compared to HPE, of ultrasonography were 70%, 100%, 100%, 88.4%, 100%, respectively and of MRI were 87.5%, 100%, 100%, 95.8%, and 96.6%, respectively.

Key-words: Magnetic Resonance Imaging (MRI), Duplex ultrasonography, Characterisation of ovarian masses, Histopathological correlation, etiological stratification

Date of Submission: 03-02-2022

Date of Acceptance: 16-02-2022

I. Introduction:

Prying open the proverbial lid of pelvis has never been simple. Encasing multisystem organs and myriads of anatomical structures, it is simply no less than a Pandora's Box. A mass within its confines, therefore, is often a cause of diagnostic dilemma. ^[1] Adenexal mass is a lump arising from structures closely related to uterus such as fallopian tube, ovaries and surrounding connective tissue. Adenexal mass can be benign or malignant. ^[2] Adenexal masses are difficult to evaluate clinically and even detailed and meticulous clinical examination leaves the clinician in doubt regarding the presence/absence of a mass, its organ of origin, and its morphological character i.e. whether it is benign, malignant or inflammatory; its extension and relation to adjacent organs. Clinically, these masses are usually detected when they become quite large to protrude out of pelvis or patient presents with symptoms like pain abdomen, bleeding per vaginum or per rectal but by this time the disease is in advanced stage. ^[1] Faced with countless conditions that may cause pelvic mass, the clinicians must often resort to a plethora of laboratory and imaging studies viz. plain films, contrast studies, ultrasonography, computed tomography and magnetic resonance imaging. It is especially among the imaging studies that confusion remains, as each modality clamours for supremacy.

The main aims of imaging are to confirm the presence of mass, determine the organ of origin, measure and characterize the mass, determine its effect on contiguous organs and to delineate the presence of metastasis, if any.^[3]

To achieve these objectives, a variety of imaging modalities are at vogue and the newer imaging modalities have almost side-lined the conventional radiological techniques practiced few years back.

Ultrasonography (US), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) are the radiodiagnostic modalities used to evaluate ovarian masses.

II. Aims And Objectives

- To assess the role of USG and MRI in the evaluation of ovarian masses.
- To assess the role of MRI in the evaluation of sonologically diagnosed indeterminate masses.
- To correlate the radiological findings with either surgical or histopathological outcome.

III. Materials And Methods

The present study was conducted in the Department of Radio-Diagnosis and Imaging, Jan Sewa Hospital, Sri Ganganagar. It was a prospective analytical cross sectional study comprising of 30 patients referred from Department of Obstetrics & Gynaecology (outpatient as well as indoor) and emergency departments of Jan Sewa Hospital, Sri Ganganagar who were clinically suspected to have pelvic lump/mass or detected with an ovarian mass incidentally on USG. Duplex Ultrasonography was done in various planes to assess the size, shape, margin, echogenicity, calcification, specific patterns, internal structure (solid/cystic/septations/wall thickness), relationship to surrounding structures and any cul-de-sac fluid. TAS was performed using 3.5-5.5 MHz curvilinear transducer through the distended urinary bladder through coupling gel for a good skin transducer contact. TVS was done using 5-8 MHz transvaginal probe in married patients whenever required. They were subjected to MR imaging with appropriate sequences with contrast administration as required. Clinical history regarding the onset of symptoms and clinical progression of the disease process were taken. Informed consent was obtained from all the subjects/guardians before the study. The spectrums of findings were recorded as per the proforma. The study was conducted after approval from institutional research and ethical committee. Imaging features documented included laterality, origin of lesion, size, shape (Regular/Irregular/Lobulated), nature (Solid/cystic/solid-cystic), wall characteristics (Thick/thin/Irregular/nodular), septal characteristics (Number, thickness, irregularity, nodule), presence of fat, calcifications & necrosis, enhancement pattern, peritoneal, mesenteric or omental deposits, lymphadenopathy & ascites. Radiological diagnosis was confirmed by histopathology, laboratory and biochemical investigations wherever possible. Ultrasonographic and MRI findings in various cases were compiled & subjected to analysis using appropriate statistical tests.

IV. Results & Discussion

Despite various advances in imaging techniques, ovarian cancer remains to be substantial threat to Indian women being the third most common neoplasm with worst prognosis among all gynecological malignancies.

Therefore, radiological evaluation is pivotal in characterization of an ovarian mass suggesting the probable etiology of the mass and distinguishing between benign and malignant masses. The results of radiologic assessments helps decide the surgeon about whether the therapeutic approach needs to be surgical or conservative.

While most lesions in the reproductive age group are fortunately benign, the prevalence of malignant lesions increases significantly with age and menopause. We found a striking prevalence of malignancy in age group >45 years. The maximum age preponderance was noted in the age group 31-40 years (33.3%) followed by 21-30 years which is closely corresponding to findings of **Sandeep J et al**. ^[4] Another study by **Jayanthan S et al** also showed similar results. ^[5]

Pre-menopausal patients predominated the study with 76.6% prevalence. Total 7 patients were proven to have malignant lesions out of which 6 (85.7%) were post-menopausal. Whereas, 1 (4.3%) out of the 23 patients with benign lesions were post-menopausal. These results corroborate with the studies done by **Arora M** et al ^[6] and **Salem F M et al**. ^[7]

Majority of the patients presented with pain abdomen as the most common clinical feature followed by menstrual irregularities (76.6% and 63.3% respectively) which very well corresponds to the studies done by **Arora M et al, De Mulder et al and Gupta K et al.** ^[6,8,9]

Majority of the ovarian masses were unilateral (76.7%) with right side predominance (56% of total) and rest were bilateral (23.3%) which is corresponding to study done by **Sandeep et al** and **Bhagat N et al**.^[4, 10]

Out of total 30 subjects with ovarian masses, 56.6% masses (17 cases) were cystic in nature, 36.7% (11 cases) were solid-cystic (mixed/complex) in morphology and 6.7% (2 cases) were purely solid in morphology. Almost similar results were found in studies done by **Jayanthan S et al**, **Prasad et al** and **Arora M et al**.^[5, 6, 11]

Valentini et al suggested criteria for characterization of suspicious adnexal lesions. Features suggestive of malignancy as per the valentine et al study were "solid, solid/cystic enhancing masses (greater than 4 cm in maximum diameter) with papillary projections and irregular thick wall and septa greater than 3 mm) into a cystic lesion" as well as a "heterogeneous and early enhancement pattern". Similar to this study, the above features in our study population also had positivity for malignancy in HPE.^[12]

Sohaib et al showed that from the analysis of the MR imaging features, "the most predictive characteristics of malignancy are vegetations/nodule in a cystic lesion, presence of ascites, a maximal diameter

greater than 6 cm, and necrosis in a solid lesion. In the same way our study also shows the presence of nodules in a cystic lesion, presence of ascites and lesion size more than 6 cm suggestive of malignancy.^[13] In our study group maximum diameter of the lesion > 6 cms was seen in 46.7% cases, Septal thickness > 3 mm in 30% cases, wall thickness > 3 mm in 26.7% cases, wall irregularities in 20%, papillary projections in 16.7% cases and central/ septal vascularity was seen in 23.3% cases.

Among these, all the cases having central and septal vascularity were found to be malignant which corresponds to the studies done by **Salem et al** and **Arora M et al**. $^{[6,7]}$

Color Doppler sonography and flow pattern analysis was carried out for each mass based. Color flow was detected in 13 out of 30 masses (43.3%). Out of these, 4 masses were benign and 7 masses were malignant. The malignant masses showed increased low resistance flow with random arrangement of abnormal blood vessels at periphery as well as in the centre of the lesion, while benign masses showed low or almost no vascularity on Colour Doppler flow imaging. Our findings correlate well with those of **Madan et al**, **Shah et al and Buy et al**. ^[14, 15, 16]

Peritoneal implants, ascites and lymphadenopathy were seen in 10%, 20% & 13.3 % cases, respectively which closely corresponds to the results inferred from the studies done by **Prasad et al** and **Jayantha S et al**. ^[17, 5]

Haemorrhagic cysts & endometriomas were the most common ovarian lesions (16.7% each) followed by dermoid (13.3%). 23 of the 30 patients (76.7%) had benign lesions while 7 (23.3%) had malignant lesions. Benign lesions include haemorrhagic cysts (16.7%), endometriomas (16.7%), mature cystic teratomas (13.3%), mucinous cystadenomas (10%), serous cystadenomas (6.7%), simple cysts (6.7%), ovarian torsion (6.7%) and tubo-ovarian masses/abscesses (6.7%). Malignant lesions include mucinous cystadenocarcinoma (6.7%), serous cystadenocarcinoma (10%), fibroma (3.3%) and dysgerminoma (3.3%). Majority of the patients had benign lesions and it is universally acknowledged that benign ovarian lesions greatly outnumber malignant ones as stated in previous study by **Jeong et al**. ^[18]

The study included 30 patients with ovarian masses. On ultrasonography, there were 26 cases of benign ovarian lesions and 4 cases of malignant ovarian tumors. MR imaging studies of 30 patients showed 24 cases to be of benign nature and 6 cases to be of malignant nature. Histopathological studies of postoperative specimens revealed 23 cases to have benign tumor and 7 cases to have malignant features.

Guerra et al study on MRI had a higher accuracy of 95% in differentiating between malignant and nonmalignant adnexal lesions. The diagnostic accuracy of our study is 96.6% similar to **Guerra et al**. ^[19] **Adumusili et al** study showed sonographically indeterminate ovarian mass lesions evaluated with MRI had a sensitivity and specificity of 100% and 94%, respectively. According to results of our study, MRI had a sensitivity of 87.5% and specificity of 100% which closely corroborates with study done by **Bhagat N et al**. ^[20, 10]

Sohaib et al study showed overall diagnostic accuracy of 91% for distinguishing MR imaging features of benign from malignant adnexal lesions. The results of our study show that the overall diagnostic accuracy of 96.6% for distinguishing benign from malignant adnexal lesions. ^[13] The one malignant lesion not detected on CEMR imaging was low grade mucinous cystadenocarcinoma. This lesion did not show septal enhancement in post contrast study. 3 malignant lesions not detected on ultrasonography include 1 case of mucinous cystadenocarcinoma (low grade) 1 case of serous papillary cystadenocarcinoma and 1 case of fibroma. In all these 3 cases colour flow on CDFI USG and post-contrast enhancement on MRI was absent.

In MRI characterization of adnexal mass lesions, enhancement of lesion, septal thickeness >3mm, nodularity of the lesion and ascites are highly suggestive of malignant nature of the lesion. In Ultrasonographic characterization of adnexal mass lesions, septal thickness, nodularity and central & peripheral vascularity of the lesion are highly suggestive of malignancy

The sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy of ultrasonography in comparison with HPE were 70%, 100%, 100%, 88.4%, 90%, respectively which correlates well with studies done by **Arora M et al** and **Bhagat N et al**. ^[6, 10]

In comparison with HPE, characterization of the detected lesions as malignant, MR imaging had a sensitivity of 87.5%, specificity of 100%, positive predictive value of 100%, a negative predictive value of 95.8%, and an overall accuracy of 96.6% which correlates well with studies done by **Arora M et al** and **Bhagat N et al**.^[6, 10]

DIAGNOSIS ON USG	NO. OF PATIENTS	PERCENTAGE
COMPLEX OVARIAN MASS	5	16.67 %
CYSTADENOMA	6	20.00 %

V. TABLES AND FIGURES TABLE - DIAGNOSIS ON USG

DERMOID	4	13.33 %
ENDOMETRIOMA	4	13.33 %
HEMORRHAGIC CYST	5	16.67 %
OVARIAN TORSION	2	6.67 %
PYOSALPINX	1	3.33 %
HYDROSALPINX	1	3.33 %
TUBO-OVARIAN MASS	2	6.67 %
TOTAL	30	100.00 %

In our study, the most common diagnosis of ovarian masses on USG was cystadenoma in 6 cases



(20%), complex ovarian mass and hemorrhagic cyst in 5 cases (16.6%) each, dermoid and endometrioma in 4 cases (13.3%) each, ovarian torsion and tubo-ovarian masses in 2 cases (6.6%) each and pyosalpinx and hydrosalpinx in 1 case (3.3%) each.

TABLE- DIAGNOS	IS ON MRI
-----------------------	-----------

DIAGNOSIS ON MRI	NO. OF PATIENTS	PERCENTAGE
COMPLEX OVARIAN MASS	1	3.33 %
COMPLEX OVARIAN MASS - UC	1	3.33 %
DERMOID	4	13.33 %
ENDOMETRIOMA	4	13.33 %
HEMORRHAGIC CYST	4	13.33 %
MUCINOUS CYSTADENOCARCINOMA	1	3.33 %
MUCINOUS CYSTADENOMA	4	13.33 %

OVARIAN TORSION	2	6.67 %
PYOSALPINX	1	3.33 %
HYDROSALPINX	1	3.33 %
SEROUS CYSTADENOCARCINOMA	3	10.00 %
SEROUS CYSTADENOMA	2	6.67 %
TUBO-OVARIAN MASS/ABSCESS	2	6.67 %
TOTAL	30	100.00 %

"Role Of Ultrasonography And Magnetic Resonance Imaging In Characterisation Of ..

MRI in our study etiologically stratified the ovarian masses as dermoid, endometrioma, hemorrhagic cyst &



mucinous cystadenoma - 4 cases (13.3%) each, serous cystadenocarcinoma in 3 cases (10%), serous cystadenoma, complex ovarian masses, ovarian torsion & tubo-ovarian masses in 2 cases (6.6%) each and mucinous cystadenocarcinoma, pyosalpinx & hydrosalpinx in 1 case (3.3%) each.



RADIOGRAPHIC IMAGES



GREY SCALE AND COLOUR DOPPLER USG IMAGES SHOWING WELL DEFINED CYSTIC LESION WITH INTERNAL SEPTATIONS AND PERIPHERAL VASCULARITY



WELL-DEFINED T2 HYPERINTENSE LESION WITH INTERNAL SEPTATIONS



WELL-DEFINED STIR HYPERINTENSE LESION WITH INTERNAL SEPTATIONS



FIGURES (A, B AND C): TAS AND CDS IMAGES SHOWING A WELL DEFINED SLIGHTLY LOBULATED SOLID MASS WITH FEW HYPOECHOIC AREAS WITHIN S/O NECROSIS. CDS SHOWS INCREASED VASCULARITY BOTH IN THE PERIPHERY AS WELL AS CENTRE OF THE MASS "Role Of Ultrasonography And Magnetic Resonance Imaging In Characterisation Of ..





FIGURES (D,E,F): MR IMAGES (T1W, T2W AXIAL AND T1 FS POST CONTRAST SAGITTAL SECTIONS) SHOWING RIGHT ADNEXAL LOBULATED MASS HYPOINTENSE ON T1 WI, INTERMEDIATE TO HIGH SIGNAL INTENSITY ON T2 WI AND HOMOGENOUS POST CONTRAST ENHANCEMENT

FIGURE (G): H & E STAINED BIOPSY SECTION SHOWING SHEETS OF TUMOR TISSUE SEPARATED BY FIBROUS SEPTA INFILTRATED BY FEW LYMPHOCYTES.





VI. Conclusion

The present study was conducted in the Department of Radio-Diagnosis and Imaging, Jan Sewa Hospital, Sri Ganganagar. It was a prospective analytical cross sectional study comprising of 30 patients referred from Department of Obstetrics & Gynaecology (outpatient as well as indoor) and emergency departments of Jan Sewa Hospital, Sri Ganganagar who were clinically suspected to have pelvic lump/mass or detected with an ovarian mass incidentally on USG.

The maximum age of preponderance was noted in the age group of 31-40 years with pain abdomen as the most common clinical feature. Majority of the ovarian masses were unilateral with right side predominance, majority being cystic in nature,

In MRI characterization of adnexal mass lesions, enhancement of lesion, septal thickeness >3mm, nodularity of the lesion and ascites are highly suggestive of malignant nature of the lesion. In Ultrasonographic characterization of adnexal mass lesions, septal thickness, nodularity and central & peripheral vascularity of the lesion are highly suggestive of malignancy. Color Doppler sonography and flow pattern analysis was carried out as an adjunct for each mass lesion. The malignant masses showed increased low resistance flow with random

arrangement of abnormal blood vessels at periphery as well as in the centre of the lesion. While benign masses showed low or almost no vascularity on Colour Doppler flow imaging. The Dynamic MR imaging features documented for evaluation include the lesion size, content of lesion (solid only, mainly solid, solid–cystic, mainly cystic, and cystic only), wall thickness, nodularity, septal thickness, early arterial phase enhancement, ascites, peritoneal implants and lymphadenopathy.

Haemorrhagic cysts & endometriomas were the most common ovarian lesions with benign ovarian lesions greatly outnumbering malignant ones. HPE correlation inferred that MRI had a higher accuracy in differentiating between malignant and non-malignant adnexal lesions and in diagnosing even sonographically indeterminate ovarian mass lesions

The sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy of ultrasonography in comparison with HPE were 70%, 100%, 100%, 88.4%, 100%, respectively. In comparison with HPE, characterization of the detected lesions as malignant, MR imaging had a sensitivity of 87.5%, specificity of 100%, positive predictive value of 100%, a negative predictive value of 95.8%, and an overall accuracy of 96.6%.

MRI diagnosed 29 out of 30 cases accurately (96.6%). MRI proved beneficial in determining the origin of pelvic mass. 3 cases misdiagnosed on USG and CDS were appropriately characterized and correctly diagnosed on MRI. Radiological diagnosis was correlated with surgical and histopathological findings

From our study we **conclude** that:

Morphological analysis of lesions like haemorrhagic cysts and endometriomas can be very well done on USG and needs no further imaging. Hydrosalpinx is well visualised in TVS as compared to TAS. Pyosalpinx cannot be diagnosed on TAS or TVS because of artifactual echoes and diffuse reflections from surrounding structures, so MRI is needed to confirm the diagnosis.

Color Doppler sonography (CDS) acts as an adjunct to USG, but as seen in our study there is a considerable overlap between spectral features benign and malignant masses, so it cannot be relied upon alone and further imaging by MRI needs to be done.

MRI is an excellent technique for detection and characterization of adnexal masses. Contrast enhanced MRI improves diagnosis in complex adnexal masses and should be used for lesions that are indeterminate on USG and CDS. The multi-planar and better soft tissue contrast imaging of MRI makes it superior imaging modality than ultrasound in evaluating adnexal masses. The ability of MRI in evaluation of adnexal masses in accurately determining the origin of a mass, internal architecture of lesions and characterizing its solid, haemorrhagic, fatty, and fibrous content may avoid unnecessary surgeries or significantly contribute to the preoperative planning of a sonography to detect indeterminate mass. Hence, this study showed that MRI was highly specific and accurate in diagnosing benign and malignant lesions which will help in future for gynecological oncologist in proper management of the patient.

Characterization of pelvic masses with multiplanar MRI aids in etiological stratification and subsequent surgical planning eventually expediting diagnosis and prompt intervention further reducing morbidity and mortality.

References

- [1]. Boldt DW and Reilly BJ. Computed Tomography of Abdominal Mass Lesions in Children. Radiology 1977; 124:371-78.
- Tewari K., Monk B. (2015) Introduction to ovarian cancer. In: The 21st Century Handbook of Clinical Ovarian Cancer. Adis, Cham. <u>https://doi.org/10.1007/978-3-319-08066-6_1</u>
- [3]. Outwater EK. Magnetic Resonance Imaging of the Pelvis. In: Haaga JR, Lanzieri CF, Gilkeson RC, editors.CT and MR Imaging of the Whole Body.4th ed. St.Louis: Mosby;2003.p.1751
- [4]. Sandeep J, Jyothi SM et al, Ultrasonographic profile of patients with ovarian tumours. Global Journal for Research analysis; 2015: 4(9); 115-116.
- [5]. Shanmuga Jayanthan S, Sathish A, Kirankumar S, Shanthi Priya K. MRI in the evaluation of adnexal masses with histopathology correlation. International Journal of Contemporary Medicine Surgery and Radiology. 2019;4(4):D39-D44.
- [6]. Arora M et al. Ovarian Masses: Hitting the Oncological Dart with Ultrasound and CT A Comparative Study in a Remote Northeast Indian Town. International Journal of Anatomy, Radiology and Surgery. 2017 Apr, Vol-6(2): RO68-RO74
- [7]. Salem FM, Alarabawy RA, El-Ebiary MT, Edorf AA, Abozeid SM. Imaging modalities in the differentiation of various adnexal lesions. Tanta Medical Journal. 2016;44(2):39-52.
- [8]. De Mulder et al, Acute Pelvic pain. The Dark Side of Radiology. 2015.
- [9]. Gupta K et al, Sonographic evaluation of acute pelvic pain. J. Evolution Med. Dent. Sci./eISSN- 2278-4802, pISSN- 2278-4748/ Vol. 5/ Issue 46/ June 09, 2016.
- [10]. Bhagat N et al, Evaluation and characterization of pelvic masses of gynaecological origin by USG, Colour Doppler and MRI in females of reproductive age group.2016.
- [11]. Arun Prasad R, Rajeev Anand, Anu Sarah Easo, Reshma Francis. Role of MRI in differentiating benign versus malignant ovarian lesions. International Journal of Contemporary Medical Research 2018;5(4):D4-D7.
- [12]. Valentin L. Prospective cross-validation of Doppler ultrasound examination and gray-scale ultrasound imaging for discrimination of benign and malignant pelvic masses. Ultrasound Obstet Gynecol.1999;14(4):273-83.
- [13]. Sohaib SA, Mills TD, Sahdev A, Webb JA, Vantrappen PO, Jacobs IJ, et al. The role of magnetic resonance imaging and ultrasound in patients with adnexal masses. Clinical Radiology. 2005;60(3):340-8.

- [14]. Madan R, Narula M K, Chitra R, Bajaj P. Sonomorphological and color Doppler flow imaging evaluation of adnexal masses. Indian J Radiol Imaging 2004;14:365-72.
- [15]. Shah D, Shah S, Parikh J, Bhatt CJ, Vaishnav K, Bala DV. Doppler ultrasound: a good and reliable predictor of ovarian malignancy. The Journal of Obstetrics and Gynecology of India. 2013;63(3):186-9.
- [16]. Buy JN, Ghossain MA, Hugol D, Hassen K, Sciot C, Truc JB, et al. Characterization of adnexal masses: combination of color Doppler and conventional sonography compared with spectral Doppler analysis alone and conventional sonography alone. Am J Roentgenol. 1996;166 (2):385-93.
- [17]. Prasad CV, Veeraswamy S et al. Efficacy of MRI and USG in the evaluation of adnexal mass lesions and correlation with histopathological examination. International Journal of Radiology and Dioagnostic Imaging; 2020: 3(1); 27-30
- [18]. Jeong YY, OutwaterEK, Kang HK. Imaging evaluation of ovarian masses.Radiographics. 2000;20:1445-70.
- [19]. Guerra A, Cunha TM, Félix A. Magnetic resonance evaluation of adnexal masses. Acta Radiologica. 2008;49(6):700-9.
- [20]. Adusumilli S, Hussain H K, Caoili EM. MRI Of Sonographically Indeterminate Adenexal Masses. Am J Roentgenol. 2006;187:732-40.

VIPIN KUMAR BAKSHI. "Role of Ultrasonography and Magnetic Resonance Imaging in Characterisation of Ovarian Masses – Histopathological Correlation and Etiological Stratification." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 21(02), 2022, pp. 22-31.